Copy for the designated Office (DO/US) PCT/GB98/02317

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HUTCHINS, Michael, Richard
Fry Heath & Spence
The Old College
53 High Street
Horley
Surrey RH6 7BN
ROYAUME-UNI

Date of mailing (day/month/year)
16 April 1999 (16.04.99)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
P57059M

International filing date (day/month/year)
31 July 1998 (31.07.98)

International application No.
PCT/GB98/02317

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ELECTROPHORETICS INTERNATIONAL PLC
Coveham House
Downside Bridge Road
Cobham
Surrey KT11 3EP
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
PROTEOME SCIENCES PLC.
Coveham House
Downside Bridge Road
Cobham
Surrey KT11 3EP
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Marie-José Devillard

Telephone No.: (41-22) 338.83.38

002573338

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HUTCHINS, Michael, Richard
Fry Heath & Spence
The Old College
53 High Street
Horley
Surrey RH6 7BN
ROYAUME-UNI

Date of mailing (day/month/year) 31 May 1999 (31.05.99)	
Applicant's or agent's file reference P57059M	**IMPORTANT NOTIFICATION**
International application No. PCT/GB98/02317	**International filing date** (day/month/year) 31 July 1998 (31.07.98)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ACHENBACH, Hans Institut für Pharmazie und Lebensmittelchemie der Universität Erlangen-Nürnberg Schuhstrasse 19 D-91052 Erlangen Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ACHENBACH, Hans Am Rheineck 7 D-65199 Wiesbaden Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Marie-José Devillard
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002643450

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 May 1999 (18.05.99)	
International application No. PCT/GB98/02317	Applicant's or agent's file reference P57059M
International filing date (day/month/year) 31 July 1998 (31.07.98)	Priority date (day/month/year) 31 July 1997 (31.07.97)
Applicant ACHENBACH, Hans	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 February 1999 (24.02.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

2623610

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*: ALL DESIGNATIONS

Regional Patent

- [x] AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [x] EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [x] EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [x] OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [x] AL Albania
- [x] AM Armenia
- [x] AT Austria
- [x] AU Australia
- [x] AZ Azerbaijan
- [x] BA Bosnia and Herzegovina
- [x] BB Barbados
- [x] BG Bulgaria
- [x] BR Brazil
- [x] BY Belarus
- [x] CA Canada
- [x] CH and LI Switzerland and Liechtenstein
- [x] CN China
- [x] CU Cuba
- [x] CZ Czech Republic
- [x] DE Germany
- [x] DK Denmark
- [x] EE Estonia
- [x] ES Spain
- [x] FI Finland
- [x] GB United Kingdom
- [x] GE Georgia
- [x] GH Ghana
- [x] GM Gambia
- [x] GW Guinea-Bissau
- [x] HU Hungary
- [x] ID Indonesia
- [x] IL Israel
- [x] IS Iceland
- [x] JP Japan
- [x] KE Kenya
- [x] KG Kyrgyzstan
- [x] KP Democratic People's Republic of Korea
- [x] KR Republic of Korea
- [x] KZ Kazakhstan
- [x] LC Saint Lucia
- [x] LK Sri Lanka
- [x] LR Liberia
- [x] LS Lesotho
- [x] LT Lithuania
- [x] LU Luxembourg
- [x] LV Latvia
- [x] MD Republic of Moldova
- [x] MG Madagascar
- [x] MK The former Yugoslav Republic of Macedonia
- [x] MN Mongolia
- [x] MW Malawi
- [x] MX Mexico
- [x] NO Norway
- [x] NZ New Zealand
- [x] PL Poland
- [x] PT Portugal
- [x] RO Romania
- [x] RU Russian Federation
- [x] SD Sudan
- [x] SE Sweden
- [x] SG Singapore
- [x] SI Slovenia
- [x] SK Slovakia
- [x] SL Sierra Leone
- [x] TJ Tajikistan
- [x] TM Turkmenistan
- [x] TR Turkey
- [x] TT Trinidad and Tobago
- [x] UA Ukraine
- [x] UG Uganda
- [x] US United States of America
- [x] UZ Uzbekistan
- [x] VN Viet Nam
- [x] YU Yugoslavia
- [x] ZW Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [ ] .....
- [ ] .....
- [ ] .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:	*in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;*
in particular:	
(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:	*in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below;*
(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents:	*in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":	*in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
(vi) if there are more than three earlier applications whose priority is claimed:	*in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:	*in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.*

Continuation of Box No. IV

FRY, Alan Valentine; SPENCE, Anne; DOWNING, Michael Philip; PRICE, Vincent Andrew; all of Fry Heath & Spence, The Old College, 53 High Street, Horley, Surrey RH6 7BN, GB.

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) GB	31 July 1997 (31.07.1997)	9716244.0	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	4	sheets
2. description	36	sheets
3. claims	11	sheets
4. abstract	1	sheets
5. drawings	4	sheets
Total	56	sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify)*:

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

M.R. Hutchins

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 307/86, C07C 49/755, C07D 317/64, A61K 35/78, 31/34, 31/12, 31/40, A01N 43/08, 31/16, 43/38

A3

(11) International Publication Number: WO 99/06388

(43) International Publication Date: 11 February 1999 (11.02.99)

(21) International Application Number: PCT/GB98/02317

(22) International Filing Date: 31 July 1998 (31.07.98)

(30) Priority Data:
9716244.0 31 July 1997 (31.07.97) GB

(71) Applicant *(for all designated States except US)*: ELECTROPHORETICS INTERNATIONAL PLC [GB/GB]; Coveham House, Downside Bridge Road, Cobham, Surrey KT11 3EP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: ACHENBACH, Hans [DE/DE]; Institut für Pharmazie und Lebensmittelchemie der Universität Erlangen–Nürnberg, Schuhstrasse 19, D–91052 Erlangen (DE).

(74) Agents: HUTCHINS, Michael, Richard et al.; Fry Heath & Spence, The Old College, 53 High Street, Horley, Surrey RH6 7BN (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
22 April 1999 (22.04.99)

(54) Title: PHARMACEUTICAL COMPOUNDS ISOLATED FROM ARISTOLOCHIA TALISCANA

(57) Abstract

The invention relates to extracts from *Aristolochia taliscana* and their uses in medicine, and also to compounds, known and novel isolated from the extracts, and compositions containing the extracts and compounds. The extracts and compounds are useful *inter alia* as anti–mutagens, antifungal agents and cytotoxic agents. The extracts and compositions of the invention can comprise at least 10 %, preferably at least 20 %, and more preferably at least 25 % by weight of a phenylbenzfuran.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/86 C07C49/755 C07D317/64 A61K35/78 A61K31/34
A61K31/12 A61K31/40 A01N43/08 A01N31/16 A01N43/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ENRIQUEZ R G ET AL: "Phytochemical investigations of plants of the genus Aristolochia, 1. Isolation and NMR spectral characterization of eupomatenoid derivatives" J. NAT. PROD. (JNPRDF,01633864);84; VOL.47 (5); PP.896-9, XP002085369 IMSS;Unidad Invest. Biomed. Med. Tradicional Herbolaria; Mexico City; 03100; Mex. (MX) see the whole document --- -/--	3-7,12, 14-23, 42-44, 51,52

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1998	26.02.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Steendijk, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 98/02317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	ENGLER T A ET AL: "Synthesis of (+-)-Licarin B and Eupomatenoids-1 and -12: A General Approach to 2-Aryl-7-alkoxy-benzofuranoid Neolignans" TETRAHEDRON LETTERS, vol. 37, no. 39, 23 September 1996, page 6969-6970 XP004030800 see the whole document	1,2,4-7, 12, 14-19, 24-44, 51,52
X	FUKUYAMA ET AL.: "Two new benzofuran-type lignans ..." CHEM.PHARM.BULL., vol. 44, no. 7, 1996, pages 1418-1420, XP002085370 see figure 1	44
X,Y	US 4 714 711 A (MILLER DOUGLAS K ET AL) 22 December 1987 see the whole document	2,4-6, 24-44, 51,52
X,Y	US 3 917 654 A (PETRACEK FRANCIS J) 4 November 1975 see the whole document	2,4-6, 24-44, 51,52
X,Y	DATABASE WPI Section Ch, Week 9005 Derwent Publications Ltd., London, GB; Class B02, AN 90-033385 XP002085374 & JP 01 311077 A (KANEBO LTD) , 15 December 1989 see abstract	2,4-6, 24-44, 51,52
X,Y	EP 0 295 851 A (MERCK FROSST CANADA INC) 21 December 1988 see the whole document	2,4-6, 24-44, 51,52
X,Y	US 3 481 944 A (MOORADIAN ARAM) 2 December 1969 see the whole document	2,4-6, 24-44, 51,52
X,Y	OHEMENG ET AL.: "Synthesis and 5-lipoxygenase inhibitory activities of some novel 2-substituted 5-benzofuran hydroxamic acids" J.MED.CHEM., vol. 37, 1994, pages 3663-3667, XP002085371 see the whole document	2,4-6, 24-44, 51,52

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 98/02317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 886 667 A (KITAGAKI KANSHIRO ET AL) 12 December 1989 see the whole document	3-7, 20-23, 42-44, 51,52
X,Y	EP 0 464 297 A (INDENA SPA) 8 January 1992 see the whole document	3-7, 20-23, 42-44, 51,52
X,Y	US 3 745 218 A (JURD L ET AL) 10 July 1973 see the whole document	3-7, 20-23, 42,44, 51,52
X,Y	CHEMICAL ABSTRACTS, vol. 89, no. 78, 23 October 1919 Columbus, Ohio, US; abstract no. 141713, CHAMBERLAIN ET AL.: "Investigations on fungicides..." XP002085373 & Ann. Appl. Biol., 1978, 88(1), 57-64 see abstract	3-7, 20-23, 42,44, 51,52
X,Y	WO 92 21669 A (SCHERING AG) 10 December 1992 see the whole document	1,4-7, 17,18, 25-44, 51,52
X,Y	DATABASE WPI Section Ch, Week 9730 Derwent Publications Ltd., London, GB; Class B02, AN 97-323149 XP002085375 & JP 09 124632 A (SANKYO CO LTD) , 13 May 1997 see abstract	1,4-7, 17,18, 25-44, 51,52
A	DATABASE WPI Section Ch, Week 8833 Derwent Publications Ltd., London, GB; Class B05, AN 88-232627 XP002085376 & JP 63 167791 A (KANEBO LTD) , 11 July 1988 see abstract	1-7,12, 14-46, 51,52

-/--

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 98/02317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 9737 Derwent Publications Ltd., London, GB; Class B02, AN 97-399459 XP002085377 & JP 09 176074 A (KIBUN SHOKUHIN KK) , 8 July 1997 see abstract	1-7,12, 14-46, 51,52
A	DATABASE WPI Section Ch, Week 9202 Derwent Publications Ltd., London, GB; Class B05, AN 92-013071 XP002085378 & JP 03 263481 A (KANEBO LTD) , 22 November 1991 see abstract	1-7,12, 14-46, 51,52
A	HIRANO ET AL.: "Suppression of mitogen-induced ..." PLANTA MED., vol. 57, 1991, pages 331-333, XP002085372 see table 1	1-7,12, 14-46, 51,52
A	EP 0 304 294 A (MONOCLONETICS INT) 22 February 1989 cited in the application see the whole document	1-7,12, 14-46, 51,52

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/02317

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4,5-7,12,14-30,31,32-43,44-46,51-52

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-4(part), 5-7, 12, 14-30(part),31, 32-43(part), 44-46, 51-52(part);

the subject-matter related to unsaturated benzofurans (antimutagenic application, antiinflammatory application, antifungal application, cytotoxic application, compounds for pharmaceutical use, compounds per se) as defined in claims

2. Claims: 1-4,6(part), 8, 14-30(part), 32-43(part), 51-52(part)

the subject-matter related to saturated benzofurans (antimutagenic application, antiinflammatory application, antifungal application, cytotoxic application, compounds for pharmaceutical use, compounds per se), as defined in claims

3. Claims: 1-3(part), 9-11, 14-24(part), 47-50, 51-52(part);

the subject-matter related to tetralones (antimutagenic application, antiinflammatory application, antifungal application, cytotoxic application, compounds for pharmaceutical use, compounds per se) as defined in claims

4. Claims: 1-3(part), 13, 14-24(part);

the subject-matter related to aristolactams (antimutagenic application, antiinflammatory application, antifungal application, cytotoxic application) as defined in claims

5. Claims: 1-3(part), 14-24(part).

the subject-matter related to other compounds isolable from Aristolochia taliscana (antimutagenic application, antiinflammatory application, antifungal application, cytotoxic application)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/GB 98/02317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4714711 A	22-12-1987	GB 2196850 A	11-05-1988
US 3917654 A	04-11-1975	NONE	
EP 0295851 A	21-12-1988	JP 1319470 A	25-12-1989
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		FR 2593396 A	31-07-1987
		GB 2184353 A,B	24-06-1987
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EP 0464297 A	08-01-1992	AT 122565 T	15-06-1995
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		AT 169295 T	15-08-1998
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		AU 1887092 A	08-01-1993
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		DE 59209444 D	10-09-1998
		EP 0516257 A	02-12-1992
		FI 935220 A	24-11-1993
		HU 65680 A	28-07-1994
		JP 6507615 T	01-09-1994
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EP 0304294 A	22-02-1989	US 4782077 A	01-11-1988
		AU 2101288 A	23-02-1989
		JP 1068320 A	14-03-1989

Form PCT/ISA/210 (patent family annex) (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

HUTCHINS, Michael, Richard
Fry Heath & Spence
The Old College
53 High Street
Horley
Surrey RH6 7BN
ROYAUME-UNI

RECEIVED
20 MAY 1999

Date of mailing (day/month/year)	
18 May 1999 (18.05.99)	
Applicant's or agent's file reference	**IMPORTANT INFORMATION**
P57059M	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB98/02317	31 July 1998 (31.07.98)	31 July 1997 (31.07.97)

Applicant
PROTEOME SCIENCES PLC. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,GM,HU,ID,IS,KE,KG,
   KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,UG,
   UZ,VN,YU,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
S. Mafla

Telephone No. (41-22) 338.83.38

2623608

WO 99/06388
PCT/GB98/02317

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
HUTCHINS, Michael, Richard
Fry Heath & Spence
The Old College
53 High Street
Horley
Surrey RH6 7BN
ROYAUME-UNI

Date of mailing (day/month/year)	
11 February 1999 (11.02.99)	
Applicant's or agent's file reference P57059M	**IMPORTANT NOTICE**
International application No. PCT/GB98/02317	**International filing date (day/month/year)** 31 July 1998 (31.07.98)
Priority date (day/month/year) 31 July 1997 (31.07.97)	
Applicant ELECTROPHORETICS INTERNATIONAL PLC et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   11 February 1999 (11.02.99) under No. WO 99/06388

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

2460740

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HUTCHINS, Michael, Richard
Fry Heath & Spence
The Old College
53 High Street
Horley
Surrey RH6 7BN
ROYAUME-UNI

RECEIVED

Date of mailing (day/month/year) 16 April 1999 (16.04.99)	
Applicant's or agent's file reference P57059M	IMPORTANT NOTIFICATION
International application No. PCT/GB98/02317	International filing date (day/month/year) 31 July 1998 (31.07.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ELECTROPHORETICS INTERNATIONAL PLC Coveham House Downside Bridge Road Cobham Surrey KT11 3EP United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
PROTEOME SCIENCES PLC. Coveham House Downside Bridge Road Cobham Surrey KT11 3EP United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Marie-José Devillard Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

02573338

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P57059M

Box No. I TITLE OF INVENTION

Pharmaceutical Compounds

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

ELECTROPHORETICS INTERNATIONAL PLC

Coveham House
Downside Bridge Road
Cobham
Surrey KT11 3EP
GB

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

ACHENBACH, Hans

Institut für Pharmazie und Lebensmittelchemie
der Universität Erlangen-Nürnberg
Schuhstrasse 19
D91052 Erlangen
Germany

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: DE

State *(i.e. country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HUTCHINS, Michael Richard

Fry Heath & Spence
The Old College
53 High Street
Horley
Surrey RH6 7BN, GB

Telephone No. +44 1293 776880

Facsimile No. +44 1293 776837

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

PATENT COOPERATION TREATY

REC'D 09 NOV 1999
WIPO PCT

PCT

18

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P57059M		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/02317	31/07/1998	31/07/1997
International Patent Classification (IPC) or national classification and IPC C07D307/86		
Applicant [ELECTROPHORETICS INTERNATIONAL PLC et al.] Proteome Sciences PLC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/02/1999	
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Steendijk, M Telephone No. +49 89 2399 8460

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/02317

I. Basis f the r p rt

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-36 as originally filed

Claims, No.:

1-52 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4(part),5-6(part),8-11,13,14-30(part),32-43(part),47-50,51-52(part).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4(part),6(part),8-11,13,14-30(part),32-43(part),47-50,51-52(part).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7,12,14-24,34-35,45-46,51-52
	No:	Claims	25-33, 36-44
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7,12,14-46,51-52
Industrial applicability (IA)	Yes:	Claims	1-7,12,14-16,21-23,25-46,51-52
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on th int rnational application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) The searched claimed subject-matter relates to unsaturated 2-phenyl-benzofurans as defined in claims. In particular this searched claimed subject matter relates to antimutagenic application (claims 1,4-7,12,14-16,17-18,25-41), antiinflammatory application (claims 2, 4-7,12,14-16,24,25-41), antifungal application (claims 3,4-7,12,14-16,20-23), cytotoxic application (claims19,25-41), compounds for pharmaceutical use (claims 42-43, 52), compounds per se (claims 44-46, 51). The preliminary international examination is restricted to this searched claimed subject-mater.

2) The documents cited in the international search report art referred to herein; the numbering (D1, D2...) corresponds to the order of citation in the search report.

D1 describes lignan type compounds isolated from Aristolochia taliscana to exhibit antibiotic activity.
D2 describes the synthesis of various lignan type compounds; D2 notes that members of this class of natural products show varied biological activity as antibacterial, cytotoxic, antiproliferative and immunosuppressant agents.
D3 describes various lignans; one compound is reported to have antioxidative (inhibition of lipid peroxidation) activity.
D4 describes 2-phenyl-benzofuran derivatives with antiinflammatory activity.
D5 describes 3-phenyl-benzofuran derivatives with antiinflammatory activity.
D6 describes 2-phenyl-benzofuran derivatives with antiinflammatory activity.
D7 describes benzofuran derivatives with antiinflammatory and cytoprotective activity.
D8 describes benzofuran derivatives with antiinflammatory and antibacterial activity.
D9 describes benzofuran derivatives with 5 lipoxygenase inhibitory activity.
D10 and D11 describe benzofuran derivatives with antifungal activity.
D12 describes benzofuran derivatives with antibiotic (incl. antifungal) activity.
D13 describes benzofuran derivatives with antifungal activity.
D14 describes benzofuran derivatives with anticancer (antiestrogen) activity.
D15 describes benzofuran derivatives with anticancer (5-alpha reductase inhibitory) activity.
D16 describes dihydrobenzofuran derivatives with anti-mutagenesis activiy.

D17 describes dihydrobenzofuran derivatives with anti-fungal and antiinflammatory activity.
D18 describes dihydrobenzofuran derivatives with anti-cancer (radical scavenging) activity.
D19 describes the antiproliferative activity of i.a. licarin B (dihydrobenzofuran derivative).
D20 describes Aristolactams (as for instance isolable from Aristolochia taliscana) for treatment of neurological disorders.

3) Novelty

3.1) Compounds per se (claims 44-46, 51).
Certain benzofuran compounds of claim 44 have been described in D3; those of claims 45-46 and 51 seem novel over the prior art.

3.2) Compounds for pharmaceutical use (claim 42-43, 52)
Benzofuran compounds for pharmaceutical use as defined in claims 42-43 (formula I as well as formula II) have been disclosed in D3,D4,D6-D15.
In this context, it is noted that as claim 42 also relates to compounds for antifungal treatment of plants. Thus this claim could actually be considered not to relate exclusively to compounds for pharmaceutical use. Accordingly, for instance compounds as disclosed in document D2 could be also considered to anticipate the subject-matter of claim 42.
It is noted that it would not appear appropriate to restore novelty of claims 42-43 by disclaimers; in view of the extensive prior art resulting claims would likely be unclear.
The subject-matter of claim 52 would appear novel.

3.3) Antimutagenic application (claims 1, 4-7, 12, 14-16, 17-18, 25-41);Cytotoxic application (claims 19, 25-41)
D14 and D15 describe the use of certain benzofurans for the treatment of cancer. Such known application seems to anticipate the subject-matter of claims 25-31.

Antiinflammatory application (claims 2, 4-7, 12, 14-16, 24, 25-41)
D4 and D6-D9 describe the use of certain benzofurans for antiinflammatory application. Such known application seems to anticipate the subject-matter of

claims 25-33,36-41.

Antifungal application (claims 3, 4-7, 12, 14-16, 20-23)
D10-D13 describe the use of certain benzofurans for antifungal application. Such known application seems to anticipate the subject-matter of claims 25-31.

Accordingly, the use of claims 25-33 and 36-41 is not considered novel.
In this context it is noted that no evidence is available indicating that any of the benzofuran compounds known in the prior art for anti-cancer, antiinflammatory or antifungal activity can be isolated for Aristolochia taliscana (claims 1-24).

4) Inventive step
In as far as the claimed subject-matter is novel over the prior art, the following observations apply concerning the requirement of inventive step.

Concerning the activity of phenylbenzofurans the present application only substantiates antimutagenic and mild cytotoxic activity for eupomatenoid-1 and 7. These compounds were already known from D1 to be isolable from Aristolochia taliscana; this document suggested testing of these compounds for pharmacological activities and already reported antibiotic activity for these compounds. Document D2 states that compounds such as those of D1 belong to class of natural products which show varied biological activity as antibacterial, cytotoxic, antiproliferative and immunosuppressant agents.
When considering the problem of providing further antimutagenic/cytotoxic agents, it would seem obvious in view of the combined teaching of D1 and D2 to test the compounds from D1 for the various indicated activities mentioned in D2 and thus arrive at the antimutagenic/cytotoxic agents of the application.

In as far as other uses and other benzofuran compounds are concerned, no furhter substantiation of any unexpected activity has been provided in view of which such subject-matter might be considered as a non-obvious solution to a technical problem. The mere isolation of various new compounds from Aristolochia taliscana cannot be considered to represent an invention / involve an inventive step, when no substantiation is provided indication that such compounds solve any technically relevant problem.

5) Industrial applicability

Claims 17-20 and 24 relate to methods of therapeutical treatment of the animal or human body ("in a substrate" as defined in claims 22-23 is here interpreted as not directed to therapeutical treatment of the human or animal body).

For the assessment of the present claims 18-20 and 24 on the question whether the subject-matter is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6) Further observations

The reference in claims 42-43 to formulae I and II is not clear as formula I and II are not defined in claims 42-43.

The combination of the definition of compounds for therapeutical uses and non-therapeutical uses in claim 42 renders the scope of these claims ambiguous. Similar applies for the combination of therapeutical and non-therapeutical applications defined in claim 3.

The relevant prior art (for instance D1 and D2) has not been mentioned in the description.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 307/86, C07C 49/755, C07D 317/64 | A2

(11) International Publication Number: WO 99/06388

(43) International Publication Date: 11 February 1999 (11.02.99)

(21) International Application Number: PCT/GB98/02317

(22) International Filing Date: 31 July 1998 (31.07.98)

(30) Priority Data:
9716244.0 31 July 1997 (31.07.97) GB

(71) Applicant *(for all designated States except US)*: ELECTROPHORETICS INTERNATIONAL PLC [GB/GB]; Coveham House, Downside Bridge Road, Cobham, Surrey KT11 3EP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: ACHENBACH, Hans [DE/DE]; Institut für Pharmazie und Lebensmittelchemie der Universität Erlangen–Nürnberg, Schuhstrasse 19, D–91052 Erlangen (DE).

(74) Agents: HUTCHINS, Michael, Richard et al.; Fry Heath & Spence, The Old College, 53 High Street, Horley, Surrey RH6 7BN (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PHARMACEUTICAL COMPOUNDS ISOLATED FROM ARISTOLOCHIA TALISCANA

(57) Abstract

The invention relates to extracts from *Aristolochia taliscana* and their uses in medicine, and also to compounds, known and novel isolated from the extracts, and compositions containing the extracts and compounds. The extracts and compounds are useful *inter alia* as anti–mutagens, antifungal agents and cytotoxic agents. The extracts and compositions of the invention can comprise at least 10 %, preferably at least 20 %, and more preferably at least 25 % by weight of a phenylbenzfuran.

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PHARMACEUTICAL COMPOUNDS ISOLATED FROM ARISTOLOCHIA TALISCANA

FIELD OF THE INVENTION

This invention relates to compounds derived from the plant *Aristolochia taliscana* and their analogues, and the uses of such compounds in medicine.

BACKGROUND OF THE INVENTION

Aristolochia taliscana, a climbing shrub found in the jungles of the southern coastal region of Mexico, is part of a family of climbing herbs and shrubs called *Aristolochiaceae*, numbering about six hundred species divided into eleven genera, and found mostly in tropical and sub-tropical regions. It is believed that the species *Aristolochia taliscana* is found only in Mexico.

Members of the *Aristolochiaceae* are known for their ability to synthesise phenanthrene alkaloids, and in particular the aristolactam alkaloids and the aristolochic acids, and arylpropanoid compounds such as the lignans and neolignans. Such compounds are disclosed in, for example, R. Hegnauer "Chemotaxonomie der Pflanzen", Vol. III, pp 184-199, Birkhäuser Verlag, Basel und Stuttgart, 1964; R. Hegnauer "Chemotaxonomie der pflanzen", Vol. VII, pp 75-83, Birkhäuser Verlag, Basel - Boston - Berlin, 1989 and F.E. Correa *et al.* "Especies Vegetales Promisorios", Vol. I, pp 440-469, Secretaria Ejecutiva del Convenio Andies Bello (SECAB), Bogota D.E. 1989, Colombia and Lopes *et al.* Rev. Latinoam. Quim., 19 (3-4), 113-17, 1988. In Lopes *et al.*, for example, the isolation of lignans from a number of different *Aristolochiaceae* is described and it is disclosed that such compounds are reported as having anti-tumour, antifungal, antibacterial and insecticidal activity. In Hinou *et al.*, J. Crude Drug Research, 1990, 28(2), 149-51, it is disclosed that aristolactam and aristolochic acid compounds isolated from *Aristolochia longa* have antibacterial activity and cytotoxic activity against P-388 lymphocytic leukaemia and human bronchial epidermoid carcinoma cells.

The isolation and characterisation of lignans, neolignans and related compounds from a wide variety of plant species has been reviewed in a series of articles by R.S. Ward, see for example Natural Product Reports, 1985, Vol. 5 pp 203-206; 1990, Vol. 7, pp 356-363; 1993, Vol. 10, pp 1-23.

However, it is clear from the available literature that the chemical structures and concentrations of arylpropanoid compounds found in *Aristolochiaceae* vary widely from one species to another. For example, in Lopes *et al.* (*idem.*), reference is made to the extraction of four Brazilian species of *Aristolochiaceae*, from which a number of dibenzyl-butyrolactone type lignans and furofuran type lignans were isolated. From studies made by the present inventors, such compounds would appear to be absent from *Aristolochia taliscana*.

Much of the work carried out on the *Aristolochiaceae* has focused on the phenanthrene alkaloid content, and in particular the aristolactam alkaloids found in the plants - see for example Crohare *et al.* Phytochemistry, 1974, Vol. 13, 1957-1962, Priestap, Phytochemistry, 1985, Vol. 24, 849-852, Talapatra *et al.* Phytochemistry, 1988, Vol. 27, 903-906 and Houghton *et al.* Phytochemistry, 1991, Vol. 10, 253-254. Houghton *et al.* suggest that compounds such as aristolochic acid, the ring-opened form of aristolactam, are of interest as immunostimulants and anticancer agents.

Crude extracts from *Aristolochia taliscana* have been known for many years to have certain medicinal properties. A book published in the 1800's, called "Las Plantas Medicinales de Mexico" (Medicinal Plants of Mexico) makes reference to the use of *Aristolochia taliscana* extracts in the treatment of snake bites and it would appear that the native tribes in this region of Mexico have known about the uses of the extracts for many centuries.

In US Patent No. 4782077 it is disclosed that an alkaloid (referred to as taliscanin) extracted from the root of *Aristolochia taliscana*, alleviates the symptoms of Parkinsonism and related neurological disorders. It is also indicated in US 4782077 that the alkaloid taliscanin may be useful in the treatment of various other neurological disorders, including Alzheimer's disease, impotency, and neurological

disorders associated with viral, bacterial, fungal and parasitic infections.

In US 4782077, an extract was prepared by pulverising *Aristolochia taliscana* root and subjecting the powder to soxhlet extraction with hexane and then benzene followed by column chromatography on an alumina column eluting with benzene-ether mixtures. The known aristolactam alkaloid taliscanin, was characterised on the basis of its melting point (272°-273°C) and its spectroscopic data.

However, the aristolactam alkaloid taliscanin has since been tested for its ability to interact with neurotransmitter receptors, and, somewhat surprisingly, exhibited 50% inhibition in only one receptor (the opiate mu receptor) out of twenty seven common receptor types tested, and exhibited very poor levels of inhibition with the remaining receptors. In particular, taliscanin exhibited negligible activity at the dopamine, GABA and serotonin receptors. These results suggest either that taliscanine exerts its neurological effects by a mechanism which is of a currently unknown type (which seems unlikely) or, perhaps, that there is another active principle in *Aristolochia taliscana* which is responsible for the reported activities.

SUMMARY OF THE INVENTION

The present applicants have been able to separate and identify the components of *Aristolochia taliscana* extracts and have found that the extract contains a substantial number of compounds other than aristolactams, in particular certain benzofuran neolignans, many of which are novel. Compounds found in the extracts have been found to have biological properties indicative of therapeutic utility. For example, benzofuran compounds isolated from taliscanine have been tested and have been found to be active as anti-mutagenic agents, as cytotoxic agents, and some have been found to have good antifungal activity. On this basis, it is anticipated that the compounds in question will find use in the treatment of tumours and other neoplastic diseases, as well as fungal infections.

Accordingly, in a first aspect, the invention provides the use of an extract of *Aristolochia taliscana* or one or more anti-mutagenically active components

isolable therefrom for the manufacture of a medicament for the treatment of disease states mediated by mutagenesis.

The invention also provides the use of an extract of an *Aristolochia* species, preferably *Aristolochia taliscana* or one or more component compounds isolable therefrom, for the manufacture of a medicament for the treatment of chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, synovitis and psoriasis.

As indicated above, component compounds of *Aristolochia taliscana* have also been found to have good antifungal activity, and in a still further aspect, the invention provides the use of an extract of *Aristolochia taliscana* or one or more antifungally active compounds isolable therefrom for the manufacture of a composition for antifungal use, for example in the treatment of plants or animals.

The invention also provides pharmaceutical compositions comprising benzofuran compounds of the type found in *Aristolochia taliscana* or benzofuran compounds analogous thereto, for example benzofuran compounds in which an aryl ring (such as an oxygenated phenyl ring) is attached to the heterocyclic ring of the benzofuran, and the uses of such compounds in medicine.

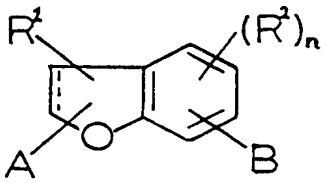
The invention also provides a novel group of benzofuran compounds having an oxygenated aryl ring (such as an oxygenated phenyl ring) attached to the heterocyclic ring of the benzofuran.

DESCRIPTION OF PREFERRED EMBODIMENTS

Compounds for use in Medicine - New Medical Uses of Known and Novel Compounds

In one preferred aspect, the invention provides the use of a compound for the manufacture of a medicament for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the treatment of chronic inflammatory conditions; the compound being of the

formula (I):



(I)

wherein the dotted line signifies a single or double bond; n is 0, 1, 2 or 3; A is a monocyclic aryl ring containing up to two heteroatoms and being optionally substituted by one or more substituent groups which may be the same or different and are selected from R^3O, R^3, R^3S, halogen; aryl and heteroaryl, wherein R^3 is hydrogen, or a hydrocarbyl group optionally substituted by a hydroxy or hydrocarbyloxy group; B is selected from carboxy, carboxaldehyde, hydrocarbyl and hydrocarbyloxy groups wherein the hydrocarbyl group is acyclic or cyclic, and optionally contains one or more heteroatoms, and is optionally substituted by one or more hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aldehyde, alkanoyl, acetal, hemiacetal and carboxy groups; R^1 is hydrogen or a hydrocarbyl group optionally including one or more heteroatoms and optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups; and R^2 is hydroxy or a hydrocarbyl or hydrocarbyloxy group optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups.

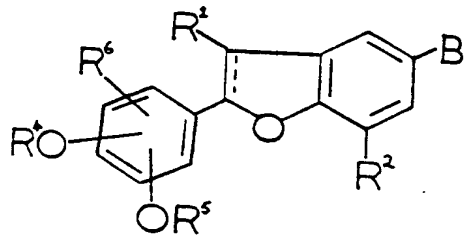
It is preferred that the monocyclic aryl ring A is attached to the 2-position of the furan ring, and it is particularly preferred that the aryl ring is a phenyl group. The phenyl ring can contain up to five substituent groups but preferably contains no more than three substituents.

Preferably, the group B is attached to the 5-position of the benzofuran group.

Preferably, there is only one group R^2, which is attached to the 7-position of the benzofuran ring.

Preferably, the dotted line signifies a double bond.

In a particularly preferred embodiment, the invention provides the use of a compound for the manufacture of a medicament for use in the treatment of the conditions described above in relation to formula (I), the compound having the formula (II):



(II)

wherein the dotted line signifies a single or double bond, B, R^1 and R^2 are as hereinbefore defined, R^4 and R^5 are the same or different and each is selected from hydrogen, C_{1-20} hydrocarbyl, C_{5-20} aryl, or C_{5-20} oxygen-containing heteroaryl; R^6 is selected from hydrogen, halogen, C_{1-20} hydrocarbyl or C_{1-20} hydrocarbyloxy optionally substituted by one or more hydroxy, alkoxy or aralkyloxy groups; or R^6 is C_{5-25} aryl or oxygen or nitrogen-containing heteroaryl.

One preferred group of compounds are the compounds in which B is C_{1-6} alkyl or alkenyl optionally substituted by one or more substituents selected from hydroxy, CHO, or R^7O wherein R^7 is a C_{1-6} alkyl or alkenyl group. More preferably, the group B is selected from $CH=CHCH_3$, $CH_2CH=CH_2$, $CH(OH)CH=CH_2$, $CH=CHCHO$, CHO, $CH=CHCH_2OH$ and $CH(OH)CH(OH)CH_3$. A particularly preferred group B is $CH=CHCH_3$.

In compounds of the formula (II) R^4 and R^5 are preferably selected from hydrogen, or C_{1-6} alkyl, or R^4 and R^5 together define an alkylene group such as $-CH_2-$. Preferably, at least one of R^4 and R^5 is hydrogen.

Particularly preferred compounds are those in which the dotted line signifies a double bond and one of R^4 and R^5 is hydrogen.

Examples of groups R^6 are hydrogen, halogen (e.g. fluoro, chloro, bromo or

iodo), C_{1-6} alkoxy (e.g. methoxy), a 2-benzofuranyl ring, or an aristolactam group.

In the foregoing formulae (I) and (II), examples of hydrocarbyl groups are aliphatic, alicyclic and aromatic groups such as alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkenyl, aryl, aralkyl, aralkenyl, aralkynyl. The hydrocarbyl groups can be optionally interrupted by one or more heteroatoms such as oxygen and sulphur.

Particular examples of alkyl groups are C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl.

Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycloheptanyl, decalinyl, adamantyl, norbornyl and bicyclooctyl.

Examples of alkenyl and alkynyl groups include vinyl, ethynyl, allyl, 1-propenyl, propargyl, but-1-enyl, but-2-enyl, but-3-enyl and 3-methylbutenyl.

Examples of cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl, and monocyclic, bicyclic and tricyclic terpene groups.

Examples of aryl groups are phenyl and naphthyl.

Examples of phenylalkyl and phenylalkenyl groups are benzyl, phenethyl, phenylpropyl, phenylbutyl and styryl groups.

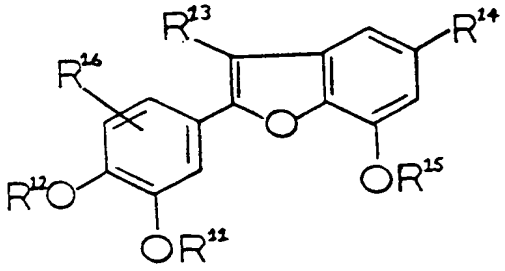
<u>First Medical Uses of Compounds Not Previously Disclosed As Having Therapeutic Utility</u>

Many compounds of the formulae (I) and (II) have not previously been disclosed as having any therapeutic uses. Accordingly, in another embodiment, the invention provides a compound of the formula (I) or (II) as hereinbefore defined for use in medicine, for example for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the

treatment of chronic inflammatory conditions, or as an anti-fungal agent in the treatment of plants or animals; but provided that when R^1 is 3-methyl, R^2 is a single methoxy group at the 7-position, and either (i) the furan ring is unsaturated and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group or a 3,4-methylenedioxyphenyl group; or (ii) the furan ring is a 2,3-dihydrofuran ring and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group, then B is other than a prop-1-enyl group attached to the 5-position of the benzfuran ring.

Novel Compounds *per se*

The present invention also provides novel compounds *per se* of the formula (III):



wherein R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} is selected from hydrogen, C_{1-6} alkyl; a cyclic terpenoid group or a group of the formula E, G or J;

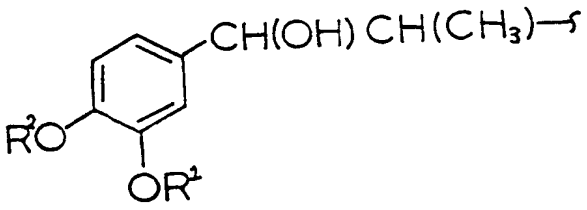
R^{13} is selected from hydrogen; C_{1-3} alkyl or hydroxy-C_{1-3} alkyl;

R^{14} is selected from CH = CH-CH_3, CH(OH)CH = CH_2, CH = CH-CHO, CH = CH-CH_2OH, CH(OH)CH(OR^{17})CH_3, or a group L;

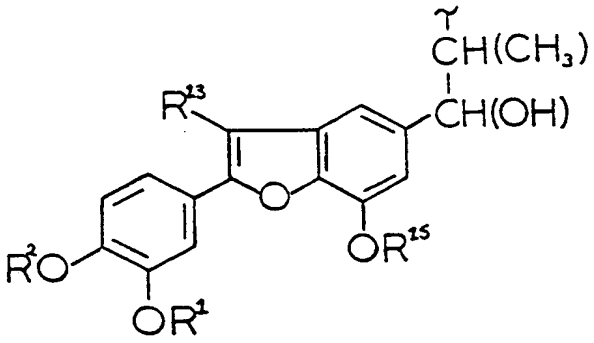
R^{15} is hydrogen or C_{1-6} alkyl;

R^{16} is hydrogen, a group M or an aristolactam group; and

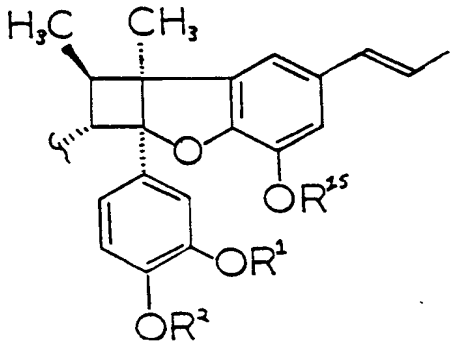
R^{17} is hydrogen or a group T; wherein the groups E, G, L, J, M and T are represented by the formulae:



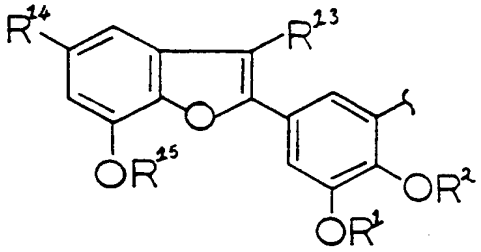
(E)



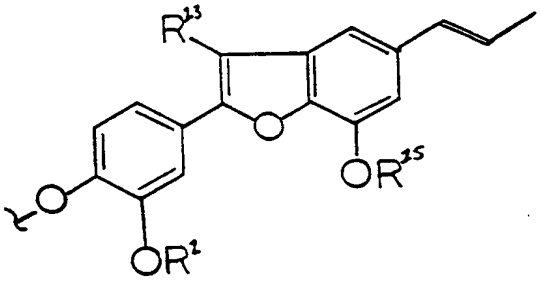
(G)



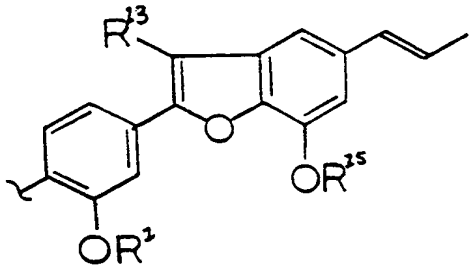
(L)



(J)



(M)

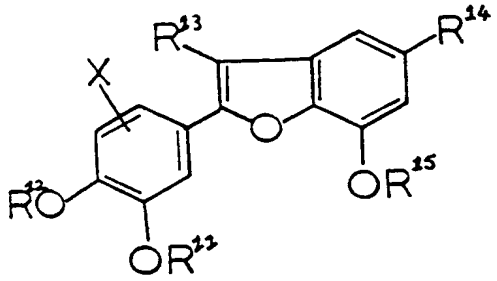


(T)

and pharmaceutically acceptable salts thereof; provided that when R^{11}, R^{13} and R^{15} are all methyl,and R^{12} and R^{16} are both hydrogen, R^{14} is selected only from $CH(OH)CH=CH_2$, $CH=CH\text{-}CHO$, $CH=CH\text{-}CH_2OH$, $CH(OH)CH(OR^{17})CH_3$ where R^{17} is a group T, or a group L.

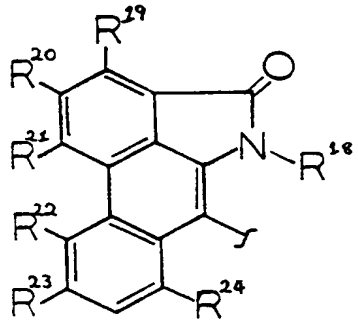
In one particular embodiment, there is provided a novel compound of the

formula (IV):



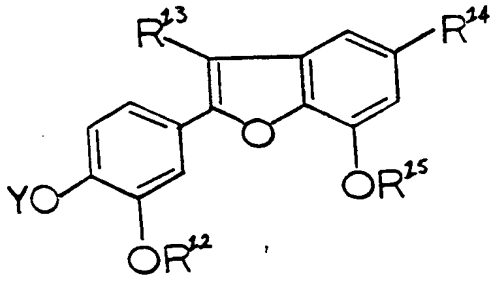
(IV)

wherein R^{11}, R^{12}, R^{13} R^{14}, R^{15} and R^{17} are as hereinbefore defined and X is a group:



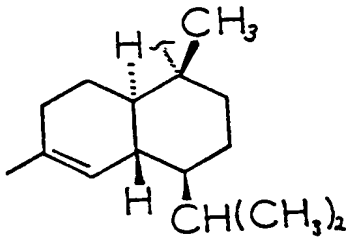
wherein R^{18} is hydrogen, benzyl or C_{1-6} alkyl; R^{19} to R^{24} are the same or different and are selected from hydrogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl and hydroxy-C_{1-6} alkyl; or any two adjacent groups together form an alkylene dioxy group.

In another embodiment, the invention provides novel compounds of the formula (V):



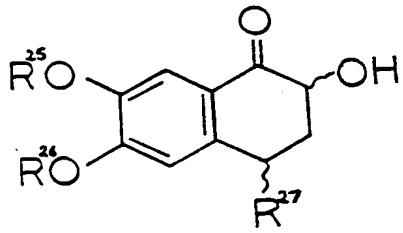
(V)

wherein Y is a monocyclic or bicyclic terpenoid group and in particular a group of the structure:



Tetralone Compounds

In a further aspect, the invention provides tetralone compounds for use in medicine, the tetralone compounds being of the formula (VI):



wherein R^{25} and R^{27} are the same or different and each is C_{1-6} alkyl, or R^{25} and R^{26} together form an alkylene group (such as methylene); and R^{26} is hydrogen or C_{1-6} alkyl.

Preferably R^{25}, R^{26} and R^{27} are all methyl.

Tetralone compounds of the formula (VI) have biocidal activity, and in particular cytotoxic, antibacterial and antifungal activity. It is therefore anticipated that they will be useful in the treatment of proliferative and infective diseases and conditions such as cancers and bacterial and fungal infections.

Accordingly, the invention also provides a compound of the formula (VI) for use in the treatment of bacterial or fungal infections, or for use in the treatment of cancers and other proliferative diseases such as psoriasis.

Compounds of the formula (VI) have previously been reported as synthetic intermediates (see Ioie *et al.* Chem. Pharm. Bull. 38, 1851-56 (1990).

Particular novel compounds of the invention are:
(±)-5-(1-Hydroxyallyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (**Compound 9**);
2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (**Compound 10**);
2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(E)-3-oxopropenyl]benzofuran (**Compound 11**);
5-Formyl-3-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (**Compound 12**);
2-(4-Hydroxy-2-methoxyphenyl)-5-[(E)-3-hydroxypropenyl]-7-methoxy-3-methylbenzofuran (**Compound 13**);
2-(3,4-Dihydroxyphenyl)-7-methoxy-3-methyl-5-(E)-propenylbenzofuran (**Compound 14**);
erythro-5-(1,2-Dihydroxypropyl)- 2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (**Compound 15**);
(2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (**Compound 19**);
erythro-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propylacetate (**Compound 22**);
threo-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propyl-acetate (**Compound 23**);
threo-1-[2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran-5-yl]-2-[4-(3-methyl-5-(e)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propan-1-ol (**Compound 24**);
2-Methoxy-4-[7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl]-6-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]phenol (Compound 25)
8.2',9.3'-Tetrahydro-bis-eupomatenoid-7 (**Compound 26**);
15-(Aristolactam-I-9-yl)-eupomatenoid-7 (**C mp und 27**);
14-O-*α*-Cadinyl-eupomatenoid-7 (**Compound 28**); and
(2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone (**C mpound 34**).

Extraction of Compounds From *Aristolochia taliscana*

Certain compounds of the formulae I to VI can be obtained by solvent extraction of plant material, such as roots, bark, leaves and twigs, from *Aristolochia taliscana* using solvents such as benzene followed by chromatographic separation of the components of the solvent extract. A typical extraction protocol is described in detail below.

Synthesis of Compounds of the Formulae I to V

The compounds of the invention, whether naturally occurring or synthetic analogues thereof can be synthesized from readily available starting materials by synthetic methods well known to those skilled in the art.

For example, compounds of the formulae (I) or (II) can be prepared by means of the reaction scheme set out in Figure 1.

The reaction conditions and reagents employed in the scheme set out in Figure 1 can be substantially as described in M. Watanabe *et al.* Chem. Pharm. Bull. 37, 2884 (1989); *ibid.* 38, 41 (1990), and *ibid.* 39, 3123 (1991), the contents of which are incorporated herein by reference.

An alternative synthetic scheme applicable to compounds of the formulae (I) or (II) wherein R^1 is a methyl group attached to the 3-position of the furan ring and A is an aryl group attached to the 2-position of the furan ring, is set out in Figure 2.

In the reaction scheme shown in Figure 2, the methoxymethylaryl ketone is reacted with the substituted *o*-hydroxybenzaldehyde in an acidic medium (for example a mixture of hydrochloric acid and acetic acid) to give a benzpyryllium salt which is then subjected to oxidation and rearrangement in the presence of hydrogen peroxide and methanol at pH 5.8 to give a benzfuran 3-carboxy ester. The benzfuran 3-carboxyester can then be treated successively with (i) lithium aluminium hydride in an ether such as diethyl ether; (ii) manganese dioxide in a non-

polar solvent such as benzene; (iii) 1,2 ethylene-dithiol, acetic acid and boron trifluoride etherate; and (iv) Raney nickel in an alcohol such as ethanol. The general conditions under which each of the above reactions can be carried out are disclosed in McCredie *et al.*, Austral. J. Chem. 22, 1011 (1969), the contents of which are incorporated herein by reference.

Pharmaceutical Uses

The extracts and compounds of the invention are useful in a number of medical aspects. In use as therapeutic agents, the compounds or extracts can be administered in standard manner, for example orally, parenterally, transdermally, rectally, via inhalation or via buccal administration. Preferably, however, they are administered orally. The dosage employed will depend on the nature and purity of the extract and the concentrations of the active principles. For an extract that has not been fractionated, the concentration administered can be in the range from 0.5mg to 500mg (dry weight) of extract per patient per day, more usually 1mg to 100mg per day. If an isolated compound or synthetic analogue thereof, or mixture of such compounds is employed, the dosages of such compounds administered typically will be similarly in the range 0.5mg to 500mg per patient per day, more usually 1mg to 100mg per day. The extracts or compounds may be administered as single doses or multiple doses as desired. The dosages of the extracts or compounds of the invention administered will depend upon *inter alia* the potency of the extract or compound, and the nature and severity of the disease state or condition under treatment but ultimately, however, will be at the discretion of the physician.

Pharmaceutical Formulations

The extracts and compounds of the invention can be formulated as solutions, syrups, tablets, capsules, lozenges, inserts, patches, powders, pills, solutions for injection or drops, or aerosols such as dry powder aerosols or liquid aerosols, by way of example. Such formulations can be prepared in accordance with methods well known *per se*.

In a particular embodiment, the compositions of the invention can take the

form of solid or semi-solid unit dosage form. For example, the compositions can take the form of tablets, granules, lozenges or capsules.

A solid or semi-solid dosage form according to the present invention can contain, for example, from 10mg to 1000mg of the extract or compounds of the invention, more typically 50mg to 500mg, e.g. 100mg to 400mg, and in particular 150mg to 350mg, particular unit dosages being approximately 200mg and 300mg.

A tablet composition will typically contain one or more pharmaceutically acceptable solid diluents, examples of which include sugars such as sucrose and lactose, and sugar alcohols such as xylitol, sorbitol and mannitol; lactose and sorbitol being particular examples.

The tablets will also typically contain one or more excipients selected from granulating agents, binders, lubricants and disintegrating agents.

Examples of disintegrants include starch and starch derivatives, and other swellable polymers, for example cross-linked polymeric disintegrants such as cross-linked carboxymethylcellulose, cross-linked polyvinylpyrrolidone and starch glycolates.

Examples of lubricants include stearates such magnesium stearate and stearic acid.

A capsule composition typically will comprise an outer shell or casing which may, for example, be formed from hard or soft forms of gelatin or gelatin-equivalents in conventional fashion. The outer shell is filled with an extract or a compound in accordance with the invention. The capsule filling may be in the form of a powder, or granules, or beads, or may be in the form of a liquid or semi-solid. Where the mixture is in the form of granules, the granules can consist of the extract or compound of the invention alone, or granulated together with a granulating agent, or they can additionally comprise a solid diluent, for example of the type set forth above.

The granules can be wet granulated or dry granulated as desired.

When the capsule filling is in liquid or semi-solid form, the extract or compound can be dissolved or suspended in a semi-solid carrier material such as a polyethylene glycol or a liquid carrier such as a glycol, e.g. propylene glycol, or glycerol. In general, it is preferred that the capsule is in solid or semi-solid form when hard gelatin capsules are used; liquid or semi-solid forms being preferred with soft gelatin capsules.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention will now be illustrated, but not limited, by reference to the following examples.

GENERAL EXPERIMENTAL DETAILS AND ISOLATION PROCEDURE

General

In the following examples, all melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on precoated plates (HPTLC plates, silica gel 50 F_{254}, Merck) using the following systems: S-1 = $CHCl_3$-MeOH (99:1), S-2 = $CHCl_3$-MeOH (96:4), S-3 = cyclohexane-EtOAc (1:1); detection: UV, anisaldehyde reagent [E. Stahl, and U. Kaltenback, Journal of Chromatography, 1961, 5, 351].

Unless otherwise stated, the optical properties and UV and IR spectra were recorded as follows: $[\alpha]_D$ in $CHCl_3$ at 20°, CD and UV in MeOH, IR in $CHCl_3$.

Unless otherwise stated, ^1H NMR were run at 360 MHz and ^{13}C NMR at 90 MHz in $CDCl_3$ with TMS as internal standard.

EIMA were obtained at 70 eV; DCIMS with NH_3 or isobutane, respectively. Apart from key ions, the only ions listed are those with relative intensities $>10\%$ and m/z >100.

Column chromatography (CC) and medium pressure liquid chromatography

(MPLC) were carried out on silica gel 60 (Macherey-Nagel) and on LiChroprep® RP 18 (40-60 μm, Merck). For CC, Fractogel PVA 500 (Merck), and Fractogel TSK HW-40 (S) (Merck) were also used.

High pressure liquid chromatography (HPLC) was performed on LiChrosorb RP 18 (7 μm, Merck).

Plant material

Roots of *Aristolochia taliscana* Hook (Aristolochiaceae) were collected by Jorge Pérez de la Rosa (Instituto Tecnologico y de Estudios Superiores de Monterrey, ITESM) from Colima (Mexico) and identified by Prof. H. Sánchez. A voucher specimen is held at the Universidad de Guadalajara, Instituto de Botanica, Guadalajara (Mexico).

EXAMPLE 1

Extraction and isolation of the Components of *Aristolochia taliscana*

Air dried, pulverized roots and rhizomes (3.5kg) of *Aristolochia taliscana* were extracted with benzene at room temperature to give 16g of a red-brown extract after removal of solvent. This extract was separated by column chromatography on Fractogel TSK HW 40 (S) with methanol to give 10 fractions (designated **A.t.1** to **A.t 10**), which were then subjected to further chromatographic separation by repeated MPLC or CC using the following systems (a) silica gel, cyclohexane-ethyl acetate gradients, (b) LiChroprep RP 18, MeOH-H_2O gradients, (c) Fractogel PVA 500, methanol. The separation scheme followed is set out in Figure 3, and the experimental conditions employed in each of the separation steps are set out in Table 2 below.

Purification and final separation was achieved by HPLC on silica gel Nucleosil 50 using cyclohexane-ethyl acetate (8:2) and high pressure liquid chromatography on silica gel RP 18 (LiChrosorb) using methanol-water mixtures, respectively. These procedures afforded the individual compounds **1** to **32** and **34** to **41** besides the mixtures **33**, **42** and **43**, whose identification was achieved by methylation or methanolysis and subsequent gas chromatographic analysis.

Table 2

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
1	A.t.1 361 mg	Silica gel 40 g	Gradient CH/EA 10/0 0/10	D 1.2 cm L 46 cm	1 246 mg = 43 2 63 mg o 3 39 mg o
2	A.t.2 431 mg	Silica gel 40 g	Gradient CH/EA 10/0 0/10	D 1.2 cm L 46 cm	1 180 mg = 33 2 232 mg o 3 15 mg o
3	A.t.3 904 mg	Silica gel 160 g	Gradient	D 2.5 cm L 46 cm	1 209 mg o 2 611 mg = A.t. 3.2
4	A.t.3.2 611 mg	Silica gel 160 g	CH/EA 7/3	D 2.5 cm L 46 cm	1 150 mg o 2 431 mg = A.t. 3.2.2
5	A.t. 3.2.2 60 mg	Nucleosil RP-18, 7μm	M/EtOH 9/1	D 2 cm L 25 cm	1 55 mg = 32 2 4 mg o
6	A.t.4 1079 mg	Silica gel 640 mg	Gradient CH/EA 10/0 0/10	D 5 cm L 46 cm	1 39 mg o 2 10 mg o 3 156 mg = A.t. 4.3 4 308 mg = A.t. 4.4 5 322 mg = A.t. 4.5 6 51 mg = A.t. 4.6
7	A.T. 43 156 mg	Nucleosil RP-18, 7μm	M/W 96/4	D 2 cm L 25 cm	1 45 mg o 2 63 mg o 3 28 mg = 38
8	A.t. 4.4 308 mg	LiChroprep RP-18, 40 g	Gradient M/W 8/2 10/0	D 1.2 cm L 46 cm	1 235 mg = A.t. 4.4.1 2 31 mg o 3 9 mg o 4 17 mg o
9	A.t. 4.4.1 120 mg	Nucleosil RP-18, 7μm	M/W 84/16	D 2 cm L 25 cm	1 90 mg o 2 28 mg = 40
10	A.t. 4.5 30 mg	Silica Gel Si 60, 10μm	H/iso-PrOH 98/2	D 2 cm L 25 cm	1 15 mg o 2 11 mg = 39
11	A.t. 4.6 51 mg	LiChroprep RP-18, 40g	M/W 8/2	D 1.2 cm L 46 cm	1 23 mg = A.t. 4.6.1 2 20 mg o
12	A.t. 4.6.1 23 mg	Nucleosil RP-18, 7μm	M/W 9/1	D 2 cm L 25 cm	1 9 mg = 37 2 5 mg o
13	A.t. 4.6.2 20 mg	Nucleosil RP-18, 7μm	M/W 98/2	D 2 cm L 25 cm	1 1 mg o 2 1 mg o 3 13 mg = 36 4 4 mg = 35

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
14	A.T. 5 784 mg	Silica gel 160 g	Gradient CH/EA 8/2 0/10	D 2.5 cm L 46 cm	1 115 mg = A.t. 5.1 2 121 mg o 3 60 mg = A.t. 5.3 4 201 mg = A.t. 5.4 5 145 mg o 6 54 mg = A.t. 5.6
15	A.t. 5.1 115 mg	PVA-500 30 g	MeOH	D 1 cm L 100 cm	1 72 mg o 2 8 mg o 3 38 mg = A.t. 5.1.3
16	A.t. 5.1.3 38 mg	PVA-500 15 g	MeOH	D 1 cm L 46 cm	1 5 mg o 2 30 mg = A.t. 5.1.3.2
17	A.t. 5.1.3.2 30 mg	Nucleosil RP-18, 7μm	M/W 95/5	D 0.8 cm L 25 cm	1 21 mg o 2 4 mg = 28
18	A.t. 5.3 60 mg	PVA-500 15 g	MeOH	D 1 cm L 46 cm	1 20 mg = A.t. 5.3.1 2 35 mg o
19	A.t. 5.3.1 20 mg	PVA-500 15 g	MeOH	D 1 cm L 46 cm	1 17 mg = 21 2 1 mg o
20	A.t. 5.4 201 mg	PVA-500 100 g	MeOH	D 2.5 cm L 100 cm	1 53 mg = 42 2 120 mg o
21	A.t. 5.6 54 mg	LiChroprep RP-18, 40 g	M/W 1/1	D 1.2 cm L 46 cm	1 18 mg = 34 2 31 mg o
22	A.t. 6 1750 mg	Silica gel 160 g	Gradient CH/EA 8/2 5/5	D 2.5 cm L 46 cm	1 3 mg o 2 1549 mg = A.t. 6.2 3 79 mg = A.t. 6.3 4 115 mg = A.t. 6.4
23	A.t. 6.2 1549 mg	LiChroprep RP-18, 160 g	M/W 7/3	D 2.5 cm L 46 cm	1 3 mg = A.t. 6.2.1 2 1540 mg = 16
24	A.t. 6.2.1 3 mg	Nucleosil RP-18, 7μm	M/W 75/25	D 2 cm L 25 cm	1 <1 mg o 2 2 mg = 6
25	A.t. 6.3 79 mg	Silica gel 9 g	$CHCl_3$	D 1 cm L 20 cm	1 30 mg = A.t. 6.3.1 2 29 mg = A.t. 6.3.2 3 11 mg = A.t. 6.3.3
26	A.t. 6.3.1 30 mg	LiChroprep RP-18, 40 g	M/W 6/4	D 1.2 cm L 46 cm	1 4 mg = 20 2 21 mg o
27	A.t. 6.3.2 29 mg	LiChroprep RP-18, 40 g	M/W 55/45	D 1.2 cm L 46 cm	1 27 mg = 31 2 2 mg = 30
28	A.t. 6.3.3 11 mg	PVA 500 15 g	MeOH	D 1 cm L 40 cm	1 <1 mg o 2 10 mg = 29
29	A.t. 6.4 115 mg	Silica gel 40 g	$CHCl_3$	D 1.2 cm L 46 cm	1 11 mg o 2 16 mg = A.t. 6.4.2 3 73 mg = A.t. 6.4.3 4 5 mg = A.t. 6.4.4

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
30	A.t. 6.4.2 16 mg	Nucleosil 40 g	M/W 6/4	D 2 cm L 25 cm	1 7 mg = 19 2 6 mg o
31	A.t. 7 6177 mg	Silica gel 640 g	CH/EA 6/4 3/7	D 5 cm L 46 cm	1 1290 mg = 17 2 4350 mg = 7 3 40 mg = A.t. 7.3 4 91 mg = A.t. 7.4 5 52 mg = A.t. 7.5 6 11 mg = A.t. 7.6 7 328 mg = A.t. 7.7
32	A.t. 7.3 40 mg	LiChroprep RP-18, 40 g	M/W 5/5 9/1	D 1.2 cm L 46 cm	1 24 mg = A.t. 7.3.1 2 7 mg o
33	A.t. 7.3.1 24 mg	LiChroprep RP-18, 40 g	M/W 3/7	D 1.2 cm L 46 cm	1 13 mg o 2 10 mg = A.t. 7.3.1.2
34	A.t. 7.3.1.2 10 mg	Nucleosil RP-18, 7μm	M/W 75.25	D 2 cm L 25 cm	1 2 mg o 2 3 mg o 3 2 mg = 12
35	A.t. 7.4 91 mg	LiChroprep RP-18, 40 g	Gradient M/W 5/5 9/1	D 1.2 cm L 46 cm	1 42 mg = A.T. 7.4.1 2 5 mg o 3 17 mg = A.t. 7.4.3 4 4 mg = 26
36	A.t. 7.4.1 42 mg	Nucleosil RP-18, 7μm	M/W 7/3	D 2 cm L 25 cm	1 3 mg o 2 7 mg = 9 3 13 mg = 10 4 <1 mg o 5 2 mg = 18
37	A.t. 7.4.3 13 mg	TSK HW 50s ca. 100 ml	MeOH	D 1 cm L 100 cm	1 11 mg = A.t. 7.4.3.1 2 1 mg o
38	A.t. 7.4.3.1 11 mg (acetylated)	LiChrosorb Si 60, 10μm	CH/EA 8/2	D 2 cm L 25 cm	1 6 mg = 22 2 3 mg = 23
39	A.t. 7.5 52 mg	LiChroprep RP-18, 40 g	Gradient M/W 5/5 9/1	D 1.2 cm L 46 cm	1 30 mg = 4 2 9 mg o
40	A.t. 7.6 11 mg	LiChroprep RP-18, 40 g	M/W 5/5	D 1.2 cm L 46 cm	1 4 mg = 13 2 6 mg o
41	A.t. 7.7 328 mg	LiChroprep RP-18, 40 mg	Gradient M/W 1/1 10/0	D 1.2 cm L 46 cm	1 4 mg = 15 2 189 mg o 3 103 mg o

Step No.	Applied to Fraction	Adsorbent	Eluent	Column dimensions	Fractions obtained
42	A.t. 8 771 mg	Silica gel 40 g	Gradient CH/EA 8/2 5/5 0/10	D 1.2 cm L 46 cm	1 384 mg = 8 2 165 mg = A.t. 8.2 3 44 mg = A.t. 8.3 4 93 mg = A.t. 8.4 5 34 mg = A.t. 8.5 6 8 mg = A.t. 8.6
43	A.t. 8.2 165 mg	LiChroprep RP-18, 40 g	M/W 75/25	D 1.2 cm L 46 cm	1 80 mg = A.t. 8.2.1 2 74 mg o
44	A.t. 8.2.1 80 mg	Silica gel 40 g	C/M 99/1	D 1.2 cm L 46 cm	1 15 mg = A.T. 8.2.1.1 2 20 mg = A.t. 8.2.1.2 3 36 mg o
45	A.t. 8.2.1.1 15 mg	PVA 500 15 g	M/C 9/1	D 1 cm L 45 cm	1 9 mg = 14 2 4 mg o
46	A.t. 8.2.1.2 20 mg	Preparative Silica gel- DC	C/M 99.5/0.5	Laufstrecke 10 cm	1 8 mg = 11 2 11 mg o
47	A.t. 8.3 44 mg	Nucleosil RP-18, 7μm	M/W 83/17	D 2 cm L 25 cm	1 7 mg = A.t. 8.3.1 2 8 mg = 5 3 19 mg o
48	A.t. 8.5 34 mg	Nucleosil RP-18, 7μm	M/W 9/1	D 2 cm L 25 cm	1 26 mg = 3 2 3 mg = 24
49	A.t. 8.6 8 mg	PVA 500 15g	MeOH	D 1 cm L 45 cm	1 3 mg - 2 2 4 mg o
50	A.t. 9 229 mg	Silica gel 80 g	Gradient CH/EA 8/2 5/5 0/10	D 2.5 cm L 23 cm	1 56 mg = A.t. 9.1 2 20 mg - A.t. 92. 3 136 mg o
51	A.t. 9.1 56 mg	Nucleosil RP-18, 7μm	M/W 96.4	D 2 cm L 25 cm	1 9 mg = 25 2 33 mg o
52	A.t. 9.2 20 mg	Nucleosil RP-18, 7μm	M/W 9/1	D 2 cm L 25 cm	1 4 mg = 1 2 13 mg o
53	A.t. 10 266 mg	Silica gel 40 g	C/M 10/0 95/5	D 1.2 cm L 46 cm	1 23 mg = A.t. 10.1 2 141 mg o 3 83 mg o
54	A.t. 10.1 23 mg	Silica gel 9 g	T/EA 6/4	D 1 cm L 18 cm	1 18 mg o 2 4 mg = 27

Abbreviations:

D: diameter, L: length, C: chloroform, CH: cyclohexane, EA: ethyl acetate, H: hexane, M: methanol, T: toluene, W: water

The compounds isolated from the benzene extract are listed below in Table 3. Those compounds already known as natural products are referred to in Table 3 by their chemical names, whilst those compounds not previously recognised as natural products are identified by code number. The full chemical names and spectroscopic and other characterising data for the new natural products are given in the paragraphs following Table 3.

Table 3

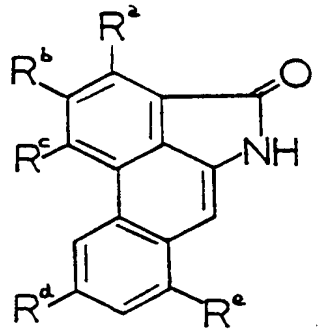
Compounds isolated from the Benzene Extract of the Root of *Aristolochia taliscana*

Compound Type	Compound (Compound No.)	Content (%)*
Alkaloid	Aristolactam I (1)*	0.03
	Aristolactam A III (2)	0.02
	Aristolactam B III (3)	0.2
	Aristolactam C III (4)	0.2
	Taliscanine (5)	0.06
Lignans	Machilin-F (6)	0.02
Neolignans		
Benzofuran-type	Eupomatenoid-7 (7)	34
	Eupomatenoid-1 (8)	3
	Compound 9	0.05
	Compound 10	0.1
	Compound 11	0.06
	Compound 12	0.02
	Compound 13	0.03
	Compound 14	0.07
	Compound 15	0.03
Dihydro-benzofuran type	( )-Licarin A (16)	12
	(-)(2S,3S)-Eupomatenoid-8 (17)	10
	(-)(2S,3S)-Machilin-B (18)	0.02
	Compound 19	0.05
	(-)(2S,3S)-5-Methoxylicarin-A (20)	0.03

Compound Type	C mpound (Compound No.)	Content (%)*
	(+)(2R,3R)-Dihydrocarinatidine (21)	0.1
Oligomers	Compound 22	0.05
	Compound 23	0.02
	Compound 24	0.02
	Compound 25	0.07
	Compound 26	0.03
Hybrids	Compound 27	0.03
	Compound 28	0.03
Phenylpropanes	Coniferyl alcohol (29)	0.08
	Ferulaaldehyde (30)	0.02
	Vanillin (31)	0.2
Sterols	Beta-sitosterol (32)	0.4
	Mixture of 3-O-acyl-beta-sitosterols (33)	1.4
Terpenoids	Compound 34	0.1
	Sandaracopimaradiene (35)	0.03
	Beta-caryophyllene (36)	0.1
	Caryophyllene oxide (37)	0.07
	ent-Germacrene-D (38)	0.2
	ent-Germacra-4(15), 5, 10 (14)-trien-1-beta-ol (39	0.09
	Spathulenol (40)	0.2
Others	D-fructose (41)	1.3
	Mixture of fatty acids (42)	0.4
	Mixture of triglycerides (43)	1.9

No aristolochic acids were detected in the extract.

The aristolactams referred to in the table have the following structural formulae:



	R^a	R^b	R^c	R^d	R^e
Aristolactam I	H	$O\text{-}CH_2\text{-}O$		H	OCH_3
Aristolactam A III	H	OH	OCH_3	OCH_3	H
Aristolactam B III	H	OCH_3	OCH_3	OCH_3	H
Aristolactam C III	CH_2OH	OCH_3	OCH_3	OCH_3	H
Taliscanine	H	OCH_3	OCH_3	OCH_3	H

Physico-chemical and Spectroscopic Properties of the Novel Natural Products (±)-5-(1-Hydroxyallyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (Compound 9).

Crystals (5 mg). Mp 164-167° (from MeOH). TLC: R_f 0.42(S-1); anisaldehyde: violet. $[\alpha]_D \pm 0°$ (c.0.1). IRν_{max} cm^{-1} :3540(OH), 3020, 1515. UVλ_{max} nm(logϵ):221(3.42), 305(3.38); +NaOH:212(3.82), 328(3,46). ^{1}H NMR(250 MHz): δ 2.00(1H,d,J = 3.5Hz,OH-8), 2.41(3H,s,Me-3),3.99(3H,s,OMe),4.03(3H,s,OMe),5.23(1H,dt,J_1 = 10.5,J_2 = 1.5Hz,H-10_B),5.31(1H,m,H-8),5.41(1H,dt,J_1 = 17,J_2 = 1.5Hz,H-10_A),5.75(1H,s,OH-14),6.14(1H,ddd,J_1 = 17,J_2 = 10.5,J_3 = 6Hz,H-9),6.83(1H,d,J = 1.5Hz,H-6),7.00(1H,d,J = 8Hz,H-15),7.12(1H,d,J = 1.5Hz, H-4, 7.29 (1H,dd,J_1 = 8,J_2 = 2Hz,H-16), 7.33(1H,d,J = 2Hz,H-12).

^{13}C NMR (60MHz):δ9.6(Me-3),56.5(2xOMe),76.5(C-8),106.6 (C-6),110.0(C-

12),110.9(C-3),111.3(C-4),114.6(C-15),116.5(C-10),121.2(C-16),124.5(C11),134.1(C3a),140.1(C-5),142.6(C-9),143.3(C-7a),146.2(C-7),148.1(C-14),149.2(C-13),152.9(C-2). EIMS m/z (rel. int.): 340[M]$^+$(100),323(14),297(11),295(11),284(12).

2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (Compound 10)

Crystals (12mg). Mp 175-179° (from MeOH). TLC:R_f0.3(S-1); anisaldehyde:grey. IRν_{max} cm^{-1}:3539(OH), 1600, 1515, 1466. UVλ_{max} nm(logϵ):231 (3.38), 266 (3.44),304 (3.34); +NaOH:240 (3.41), 295(3.25), 328(3.3). ^{1}H NMR (250 MHz): δ1.57(1H,t,J=4Hz, OH-3), 1.90(3H,dd,J_1=6.5J_2=1.5Hz, Me-10), 3.95(3H,s,OMe),4.04(3H,s,OMe),4.91(2H,d,J=4Hz,CH_2OH),5.81(1H,s,OH-14), 6.23(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.48(1H,dq,J_1=16,$J_2$1.5Hz,H-8), 6.83(1H,d,J=1.5Hz,H-6), 7.01(1H,d,J=8Hz,H-15), 7.18(1H,d,J=1.5Hz,H-4), 7.38(1H,dd,J_1=8,J_2=2Hz,H-16), 7.41(1H,d,J=2Hz,H-12). ^{13}C NMR:δ18.4(Me-10), 55.7(CH_2OH), 56.1(2xOMe), 104.8(C-6), 109.0(C-4), 110.0(C-12), 113.8(C-3), 114.7(C-15), 121.3(C-16), 122.4(C-11), 124.8(C-9), 131.2(C-3a), 131.3(C-8), 123.3(C-5), 142.3(C-7a), 145.0(C-7), 146.6(C-14), 146.7(C-13), 154.6(C-2). EIMS m/z(rel.int):340[M]$^+$(100), 323(15),291(19),151(10).

2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(E)-3-oxopropenyl]benzofuran (Compound 11)

Crystals (8 mg). Mp 169-170° (from MeOH). TLC:R_f0.39(S-1); anisaldehyde:blue. IR ν_{max} cm^{-1}:3538(OH), 1672(CO), 1610, 1514. UV λ_{max} nm(logϵ):213(4.04), 291(4.91), 314(4.31); +NaOH:215(4.93), 337(4.36). ^{1}H NMR(250MHz):δ2.46(3H,s,Me-3), 3.99(3H,s,OMe), 4.08(3H,s,OMe), 6.73(1H,dd,J_1=16,J_2=8Hz,H-8), 7.00(1H,d,J=2Hz,H-6), 7.04(1H,d,J=2Hz,H-15), 7.30(1H,d,J=8Hz,H-16), 7.32(1H,dd,J_1=8,J_2=2Hz,H-12), 7.33(1H,d,J=2Hz,H-4), 7.58(1H,d,J=16Hz,H-8), 9.72(1H,d,J=8Hz,CHO). ^{13}CNMR(60MHz):δ9.5(Me-3), 56.1(2xOMe), 105.7(C-6), 109.6(C-12), 110.1(C-3), 113.8(C-4), 114.7(C-15), 120.8(C-16), 122.9(C-11), 124.5(C-9), 129.7(C-5), 133.5(C-3a), 144.7(C-7a), 145.4(C-7), 146.3(C-14), 146.8(C-13), 152.6(C-2), 153.9(C-8), 193.6(C-10). EIMS m/z (rel. int.):338[M]$^+$(96), 311(19), 310(100), 295(28), 267(29), 178(10), 169(12), 165(12), 152(11).

5-Formyl-3-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (Compound 12)

Crystals (2 mg). Mp 162-165° (from MeOH). TLC:R_f0.43(S-1); anisaldehyde:light blue. IRν_{max} cm^{-1}:3540(OH), 3023, 1688(CO), 1515. UV λ_{max} nm(logϵ):231(4.40), 283(4.61), 307(sh,4.53); +NaOH:240(4.44), 329(4.62). ^{1}H NMR:δ2.48(3H,s,Me-3), 4.00(3H,s,OMe), 4.07(3H,s,OMe), 5.80(1H,s,OH), 7.03(1H,d,J=8Hz,H-15), 7.32(1H,dd,J_1=8, J_2=2Hz,H-16), 7.33(1H,d,J=2Hz,H-12), 7.37(1H,d,J=1.5Hz,H-4), 7.68(1H,d,J=1.5Hz,H-6), 10.0(1H,s,CHO). ^{13}C NMR: δ9.5(Me-3), 56.1(2xOMe), 104.7(C-6), 110.5(C-3), 114.6(C-4), 117.4(C-15), 120.8(C-16), 122.8(C-11), 132.9(C-3a), 133.1(C-5), 145.8(C-7), 146.2(C-14), 146.4(C-13), 146.8(C-7a), 153.0(C-2), 192.0(CO). EIMS m/z (rel. int.):312[M]$^+$(100), 297(14), 269(12), 156(15).

2-(4-Hydroxy-3-methoxyphenyl)-5-[(E)-3-hydroxypropenyl]-7-methoxy-3-methylbenzofuran (Compound 13)

Crystals (7 mg). Mp 180-183° (from MeOH).

TLC:R_f0.16(S-1); anisaldehyde:violet. IRν_{max} cm^{-1}:3540(OH), 3020, 1612, 1515. UV λ_{max} nm(logϵ):232(3.16), 271(3.30), 306(sh 3.23); +NaOH:240(3.29), 291(3,19), 329(3.33). ^{1}H NMR δ1.45(1H,t,J=5.5Hz, OH-10), 2.41(3H,s,Me-3), 3.99(3H,s,OMe), 4.05(3H,s,OMe), 4.35(2H,dd,J_1=5.5,J_2=1Hz,CH_2OH), 5.75(1H,s,OH-14), 6.37(1H dt,J_1=16,J_2=5.5Hz,H-9), 6.71(1H,dt,J_1=16,J_2=1Hz,H-8), 6.88(1H,d,J=1.5Hz,H-6), 7.00(1H,d,J=8.5Hz,H-15), 7.11(1H,d,J=1.5Hz,H-4), 7.29(1H,dd,J_1=8.5,J_2=2Hz,H-16), 7.32(1H,d,J=2Hz,H-12). ^{13}C NMR:δ9.6(Me-3), 56.1(2xOMe), 63.8(C-10), 104.8(C-6), 109.5(C-4), 110.2(C-3 and C-12), 114.4(C-15), 120.7(C-16), 123.5(C-11), 127.2(C-9), 132.1(C-8), 132.3(C-3a), 133.2(C-5), 142.6(C-7a), 145.0(C-7), 145.8(C-14), 146.6(C-13), 151.8(C-2). EIMS m/z (rel. int.): 340[M]$^+$(100), 312(12), 311(20), 297(22), 284(37), 282(15), 281(12), 279(11), 165(13), 151(14), 149(10), 55(10).

2-(3,4-Dihydroxyphenyl)-7-methoxy-3-methyl-5-(E)-propenylbenzofuran (Compound 14)

Oil (9 mg). TLC:R_f0.15(S-2); anisaldehyde:grey. IR ν_{max} cm^{-1}:3548(OH), 3015, 1600, 1523, 1483. UV λ_{max} nm(logϵ):231(4.49), 264(4.59), 207(sh.4.46);

+ NaOH: 242 (4.60), 327 (4.44). ^{1}H NMR (CD_3OD, 250 MHz): δ1.88 (3H, dd, $J_1 = 6.5$, $J_2 = 1.5$Hz, Me-10), 2.37 (3H, s, Me-3), 4.01 (3H, s, OMe), 6.22 (1H, dq, $J_1 = 16$, $J_2 = 6.5$Hz, H-9), 6.47 (1H, dq, $J_1 = 16$, $J_2 = 1.5$Hz, H-8), 6.85 (1H, d, J = 1.5Hz, H-6), 6.88 (1H, d, J = 8.5Hz, H-15), 7.01 (1H, d, J = 1.5Hz, H-4), 7.14 (1H, dd, $J_1 = 8.5$Hz, $J_1 = 2$Hz, H-16), 7.26 (1H, d, J = 2Hz, H-12). ^{13}C NMR (CD_3OD, 60MHz): δ9.6 (Me-3), 18.6 (Me-10), 56.7 (OMe), 105.8 (C-6), 110.1 (C-4), 110.5 (C-3), 114.9 (C-12), 116.6 (C-15), 119.9 (C-16), 124.5 (C-11), 124.8 (C-9), 132.9 (C-8), 134.4 (C-3a), 135.1 (C-5), 143.3 (C-71), 146.2 (C-7), 146.5 (C-14), 146.9 (C-13), 152.9 (C-2). EIMS m/z (rel. int.): 310 $[M]^+$ (100), 309 (10).

erythro-5-(1,2-Dihydroxypropyl)- 2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran (Compound 15)

Amorphous (3 mg). TLC: R_f 0.16 (S-2); anisaldehyde: violet. $[\alpha]_D$ + 17° (c0.2). IR ν_{max} cm^{-1}: 3435 (OH), 2927, 1655, 1516, 1462. UV λ_{max} nm (logϵ): 216 (4.16), 304 (4.04): + NaOH: 211 (4.80), 328 (4.11). ^{1}H NMR: δ1.11 (3H, d, J = 6.5Hz, Me-10), 2.42 (3H, s, Me-3), 2.44 (1H, br d, J = 3Hz, O<u>H</u>-9), 2.61 (1H, br d, J = 3HZ, O<u>H</u>-8), 3.90 (1H, m, H-9), 3.99 (3H, s, OMe), 4.05 (3H, s, OMe), 4.48 (1H, dd, $J_1 = 7.5$, $J_2 = 3$Hz, H-8), 5,75 (1H, s, O<u>H</u>-14), 6.80 (1H, d, J = 1.5Hz, H-6), 7.01 (1H, d, J = 8Hz, H-15), 7.10 (1H, d, J = 1.5Hz, H-4), 7.30 (1H, dd, $J_1 = 8$, $J_2 = 2$Hz, H-16), 7.33 (1H, d, J = 2Hz, H-12). ^{13}C NMR (60MHz): δ9.6 (Me-3), 16.9 (Me-10), 56.1, 56.2 (2xOCH_3), 72.5 (C-9), 80.1 (C-8), 105.3 (C-6), 109.5 (C-12), 109.9 (C-4), 110.1 (C-3), 114.5 (C-15), 120.7 (C-16), 123.5 (C-11), 133.0 (C-3a), 136.4 (C-5), 142.5 (C-7a), 145.0 (C-7), 145.9 (C-14), 146.6 (C-13), 152.6 (C-2). EIMS m/z (rel.int.): 358 $[M]^+$ (100), 328 (16), 314 (21), 313 (81), 285 (52), 258 (11), 257 (57), 253 (28), 225 (14), 133 (13).

(2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran (Compound 19) Amorphous (6 mg). TLC: R_f 0.3 (S-1); anisaldehyde: red. $[\alpha]_D$ + 65° (c.0.2). CD λ_{max} nm$\Delta\epsilon$): 235 (-3.15), 260 (+3.14), 285 (+2.39). IR ν_{max} cm^{-1}: 3543 (OH), 3019, 1613, 1518, 1499, 1466. UV λ_{max} nm (logϵ): 204 (4.59), 218 (4.49), 273 (4.23); + NaOH: 211 (4.93), 268 (4.38). ^{1}H NMR (CD_3OD): δ1.78 (3H, dd, $J_1 = 6$, $J_2 = 2$Hz, Me10), 3.47 (1H, m, H-3), 3,78 (2H, d, J = 7Hz, C<u>H_2</u>OH), 3.80 (3H, s, OMe), 3.86 (3H, s, OMe), 5.50 (1H, d, J-6Hz, H-2), 6.11 (1H, dq, $J_1 = 16$, $J_2 = 6.5$Hz, H-9), 6.33 (1H, dq, $J_1 = 16$, $J_2 = 2$Hz, H-8), 6.76 (1H, d, J = 8Hz, H-15), 6.82 (1H, dd, $J_1 = 8$, $J_2 = 2$Hz, H-16), 6.86 (1H, br s, H-4),

6.88(1H,br s,H-6), 6.94(1H,d,J = 2Hz,H-12). ^{13}C NMR(60MHz):18.3(Me-10), 53.7(C-3), 56.0(2xOMe), 64.0(CH_2OH-3), 88.7(C-2), 108.8(C-12), 110.0(C-6), 113.9(C-4), 114.3(C-15), 119.4(C-16), 123.8(C-9), 127.9(C-11), 129.7(C-8), 132.3(C-5), 133.0(C-3a), 144.4(C-7), 145.7(C-14), 146.7(C-7a), 147.6(C-13), EIMS m/z (rel.int.):342[M]$_+$(52), 324(78), 310(20), 309(100), 293(28), 292(32), 221(10), 165(14), 152(13), 151(22), 137(17).

erythro-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propylacetate (Compound 22)

Colourless crystals (5 mg). MP 156-158° (from MeOH). TLC:R_f0.54(S-3); anisaldehyde:grey. $[\alpha]_D$ + 18°(c.0.1). IRν_{max} cm^{-1}:3018, 1762,1741,1510. UV λ_{max} nm(logϵ):226(4.08), 266(4.10), 308(4.08). ^{1}H NMR:δ1.31(3H,d,J = 6.5Hz, Me-9'), 1.89(3H,dd,J_1 = 6.5,J_2 = 1.5Hz,Me-10), 2.11(3H,s,MeCO-7'), 2.25(3H,s,MeCO-4'), 2.40(3H,s,Me-3), 3.83(3H,s,OMe), 3.89(3H,s,OMe), 4.01(3H,s,OMe), 4.77(1H,m,H-8'), 5.91(1H,d,J = 4.5Hz,H-7'), 6.24(1H,dq,J_1 = 16,J_2 = 6Hz,H-9), 6.50(1H,dq,J_1 = 16,J_2 = 1.5Hz,H-8), 6.80(1H,d,J = 1.5Hz,H-6), 6.91(1H,d,J = 8Hz,H-15), 6.96(1H,d,J = 8.5Hz,H-6'), 6.97(1H,dd,J_1 = 8.5, J_2 = 2HzH-5'), 7.01(1H,br s,H-4), 7.08(1H,d,J = 2Hz,H-2'), 7.29(1H,dd,J_1 = 8,J_2 = 2Hz,H-16), 7.32(1H,d,J = 2Hz,H-12). ^{13}C NMR:δ9.6(Me-3), 15.5(Me-9'), 18.4(Me-10), 20.7(MeCO-4'), 21.2(MeCO-7'), 56.0,56.1(3xOMe), 76.6(C-7'),78.0(C-8'),104.7(C-6),109.2(C-4),110.8(C-3),111.3(C-12),112.1(C-2'),117.7(C-5'),119.6(C-15),119.9(C-6'),122.4(C-16),124.4(C-9),125.8(C-11), 131.5(C-8), 133.0(C-3a), 133.7(C-5), 135.9(C-1'), 139.6(C-14'), 142.2(C-7a), 144.9(C-7), 147.1(C-14), 150.9(C-13), 151.3(C-3'), 168.9(MeCO-4'), 169.9(MeCO-7'). EIMS m/z (rel.int.):588[M]$_+$(6), 366(14), 325(20), 324(100), 265(31), 223(54), 181(27), 164(25).

threo-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propyl-acetate (Compound 23)

Mp 155-158° (from MeOH). TLC:R_f0.54(S-3); anisaldehyde:grey. $[\alpha]_D$ + 35°(c.0.1). IRν_{max} cm^{-1}:3018,1762,1741,1510. UV λ_{max} nm(logϵ):226(4.08), 266(4.10), 308(4.08). ^{1}H NMR:δ1.24(3H,d,J = 6.5Hz,Me-9'). 191(3H,dd,J_1 = 6.5, J_2 = 2Hz,Me-10), 2.04(3H,s,MeCO-7'), 2.30(3H,s,MeCO-4'), 2.43(3H,s,Me-3), 3.85(3H,s,OMe), 3.92(3H,s,OMe), 4.04(3H,s,OMe),

4.65(1H,m,H-8'), 5.99(1H,d,J = 6.5Hz,H-7'), 6.22(1H,dq,J_1 = 16,J_2 = 6.5Hz, H-9), 6.50(1H,dq, J_1 = 16,J_2 = 2Hz,H-8),6.84(1H,d,J = 1.5Hz,H-6), 6.99(1H,dd,J_1 = 8,J_2 = 2Hz, H-16), 7.02(1H,d,J = 8Hz,H-15), 7.03(1H,d,J = 1.5Hz,H-4), 7.03(1H,d,J = 8.5Hz H-15'), 7.04(1H,d,J = 2Hz,H-12), 7.31(1H,dd,J_1 = 8.5,J_2 = 2Hz,H-16'), 7.35(1H,d,J = 2Hz,H-12'), ^{13}CNMR:δ9.6(Me-3), 16.7(Me-9'), 20.7(MeCO-4'), 21.1(MeCO-7'), 56.0,56.1(3xOMe), 76.6(C-7'), 77.8(C-8'), 104.6(C-6), 109.2(C-4), 110.7(C-3), 111.2(C-12), 111.9(C-2'), 116.8(C-5'), 119.8(C-15), 119.9(C-6'), 122.7(C-16), 124.4(C-9), 125.5(C-11), 131.5(C-8), 133.0(C-3a), 133.7(C-5), 136.0(C-1'), 139.8(C-4'), 142.2(C-7a), 144.9(C-7), 147.8(C-14), 150.5(C-2), 151.0(C-13), 151.2(C-3'), 168.8(MeCO-4'), 169.9(MeCO-7'). EIMS m/z (rel.int.):588[M]$_+$(6), 366(15), 325(20), 324(100), 265(30), 223(54), 181(27), 164(25).

threo-1-[2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran-5-yl]-2-[4-(3-methyl-5-(e)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propan-1-ol (Compound 24)

Amorphous (3mg). TLC:R_f0.69(S-2); anisaldehyde:violet. $[\alpha]_D$ + 20°(c.0.2). IRν_{max} cm^{-1}:3540(OH),3020,2938,1614,1511,1466. UVλ_{max} nm(logϵ):229(4.16), 266(4.20), 308(4.14); +NaOH: 239(4.43), 330(4.46). ^{1}H NMR: δ0.98(3H,d,J = 6.5Hz,Me-10'), 1.89(3H,dd,J_1 = 6.5, J_2 = 1.5Hz,Me-10), 2.36(3H,s,Me-3'), 2.43(3H,s,Me-3),3.98,4.01,4.02,4.06 (12H,s.4xMe), 4.22(1H,m,H-9'), 4.69(1H,d,J = 8.5Hz,H-8'), 5.74(1H,s,OH-14'), 6.20(1H,dq,J_1 = 16,J_2 = 6.5Hz,H-9), 6.48(1H,dq,J_1 = 16,J_2 = 1.5Hz-H-8), 6.81(1H,d,J = 8.5Hz,H-15), 6.81(1H,d,J = 1.5Hz,H-6), 6.89(1H,d,J = 1.5Hz,H-6'), 7.00(1H,d,J = 8Hz,H-15'), 7.01(1H,d,J = 1.5Hz,H-4), 7.07(1H,dd,J_1-8.5, J_2 = 2Hz,H-16), 7.09(1H,d,J = 1.5Hz,H-4'), 7.29(1H,dd, J_1 = 8.5,J_2 = 2Hz,H-16'), 7.31(1H,d,J = 2Hz,H-12'), 7.35(1H,d,J = 2Hz,H-12). ^{13}CNMR:δ9.6(Me-3), 9.7(Me-3'), 18.0(Me-10'), 18.4(Me-10), 56.0, 56.1,56.3(4xOMe), 71.8(c-9'), 91.3(C-8'), 104.7(C-6), 105.4(C-6'), 109.2(C-4), 109.6(C-12'), 110.2(C-12), 110.4(c-4'), 110.6(C-3), 110.9(C-3'), 114.5(C-15), 118.5(C-15'), 119.8(C-16), 120.8(C-16'), 123.2(C-11'), 124.5(C-9), 126.2(C-11), 131.4(C-8), 132.9(C-31'), 133.1(C-3a), 133.7(C-5), 133.9(C-5'), 142.2(C-7a), 142.6(C-7a'), 144.9(C-7), 145.2(C-7'), 145.9(C-14'), 146.6(C-13'), 147.9(C-4), 150.7(C-13), 151.1(C-2'), 151.9(C-2). DCIMS m/z (rel.int.):665[m + h]$^+$(10), 381(9), 367(12), 343(12), 342(25),

341(100), 340(24), 326(22), 325(94), 324(44).

2-Methoxy-4-[7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl]-6-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]phenol (Compound 25)

Amorphous (9 mg). TLC:R_f0.83(S-1); anisaldehyde:grey. IRν_{max} cm^{-1}:3538(OH), 3020, 2939, 1613, 1599, 1510. UV λ_{max} nm(logϵ):233(4.14),267(4.48),309(4.46); +NaOH:215(5.23), 316(4.41). ^{1}H NMR(250 MHz):δ1.91(6H,m,Me-10 and Me10'), 2.31(3H,s,Me-3'), 2.42(3H,s,Me-3),3.99,4.01,4.04(12H,s,4xOMe), 6.20(2H,m,H-9 and H-9'),6.47(1H,dq,J_1 = 16,J_2 = 1.5Hz,H-8'), 6.50(1H,dq,J_1 = 16,$_2$ = 1.5Hz,H-8),6.81(1H,d,J = 1.5Hz,H6'),6.84(1H,d, J = 1.5Hz,H-6),7.00(1H,d,J = 1.5Hz,H-4'),7.03(1H,d,J = 1.5Hz,H4),7.04 (1H,d,J = 2Hz,H-12'),7.05(1H,d,J = 8Hz,H-15),7.18(1H,d,J = 2Hz,H16'), 7.31(1H,dd,J_1 = 8,J_2 = 2Hz,H-16),7.45(1H,d,J = 2Hz,H12). ^{13}C NMR(60MHz): δ9.5,9.6(Me-3,Me-3'), 18.4(Me-10,Me-10'), 56.1,56.3,56.5(4xOMe), 104.7,104.8(C-6,C-6'), 106.1(C-16'), 109.3,109.8(C-4,C-4'), 111.2(C-3'), 111.3(C-12), 111.5(C-3), 111.9(C-12'), 116.8(C-15), 119.9(C-16), 122.8(C-11), 124.4,124.5(C-9,C-9'), 127.6(C-11'), 132.7,132.9(C-8,C-8'), 133.7,133.8(C-3a,C-3a'), 137.3(C-14'), 142,1,142.3(C-71,C-7a'), 143.8(C-14), 144.8,144.9(C-7,C-7'), 145.8(c-15'), 148.2(C-13,C-13'),150.4, 150.9(C-2,C-2'). DCIMS m/z (rel.int.):647[M+H]$^+$(100), 646(44), 473(18), 369(12), 341(26), 339(16), 326(11), 325(46), 324(23), 309(34), 308(13), 283(20), 113(19), 107(18), 105(12).

8.2',9.3'-Tetrahydro-bis-eupomatenoid-7 (Compound 26)

Crystals (4 mg). Mp 175-179° (from MeOH). TLC:R_f0.26(S-1); anisaldehyde:grey-blue. $[\alpha]_D$ ± 0°(c.0.1). IRν_{max} cm^{-1}:3540(OH), 3020,1618,1465. UV λ_{max} nm(logϵ) 217(5.03), 279(4.83), 297(sh 4.79), +NaOH: 261(4.76), 305(4.75), 327(sh 4.78). ^{1}H NMRδ1.05(3H,s,Me-3'), 1.31(3H,d,J = 6.5Hz,Me-10), 1.86(3H,dd,J_1 = 6.5,J_2 = 1.5Hz,Me-10'), 2.37(3H,s,Me-3),2.97(1H,dq, J_1 = 11,J_2 = 6.5Hz,H-9), 3.50(3H,z,OMe-13'), 3.76(1H,d,J = 11Hz,H-8), 3.80(3H,s,OMe-7), 3.92(3H,s,OMe-13'), 4.00(3H,s,OMe-7'), 6.17(1H,dq, J_1 = 16,J_2 = 6.5Hz,H-9'), 6.42(1H,dq,J_1 = 16,J_2 = 1.5Hz,H-8'), 6.48(1H,s,H-6), 6.63(1H,d,J = 8.5Hz,H-15'), 6.75(1H,d,J = 2Hz,H-12'), 6.83(1H,dd, J_1 = 8.5, J_2 = 2Hz,H-16'),6.85(1H,d,J = 1.5Hz,H-4'),6.90(1H,d,J = 8Hz,H-15),6.94(1H,s,H-

4), 6.98(1H,d,J = 1.5Hz,H-6'), 7.22(1H,dd,J_1 = 8,J_2 = 2Hz,H-16), 7.33(1H,d,J = 2Hz,H-12). ^{13}C NMR:δ9.6 (Me-3), 16.2(Me-10), 18.5(Me-10'), 22.1(Me-3'), 42.7(C-9), 56.2(C-3'), 56.5,56.7,57.3,58.2(4xOMe), 98.1(C-8), 107.9(C-2'), 109.7(C-6), 110.6(C-4), 110.9(C-6'), 111.3(C-12), 111.8(C-4'), 115.5(C-15'),116.5(C-15),117.4(C-12'),120.7(C-16'),121.2(C-16),124.1(C-9'), 124.5(C-11), 128.8(C-11'), 132.4(C-8'), 133.7(C-5'), 134.0(C-3a), 135.3(C-5), 136.0(C-3a'), 142.5(C-7a), 146.0(C-7), 146.4(C-7'), 146.9(C-13'), 147.7(C-7a'), 148.0(C-14'), 149.2(C-14), 152.6(C-2). CIMS m/z (rel.int.):649[M+H]$^+$ (13), 648(7), 367(12), 326(25), 325(100), 324(88).

15-(Aristolactam-I-9-yl)-eupomatenoid-7 (Compound 27)

Yellow crystals (4 mg). Mp 165-170° (from MeOH). TLC:R_f0.43(S-2); anisaldehyde:green. IRν_{max} cm^{-1}:3531,3442,3020,3011,1699,1610,1482,1466. UV λ_{max} nm(logϵ):256 (4.83), 267(sh 4.79), 301(4.73), 405(4.00). ^{1}H NMR (C_5D_5N):δ1.86 (3H,dd,J_1 = 6.5,J_2 = 1.5Hz,Me-10), 2.44(3H,s,Me-3), 3.52(3H,s,OMe-8'), 3.80(3H,s,OMe-13), 3.96(3H,s,OMe-7), 6.30(1H,dq,J_1 = 16,J_2 = 6.5Hz,H-9), 6.34(2H,d,J = 1Hz,OC$\underline{H_2}$O), 6.63(1H,dq,J_1 = 16,J_2 = 1.5Hz,H-8), 7.09(1H,d,J = 1.5Hz,H-6), 7.13(1H,dd,J_1 = 8,J_2 = 1Hz,H-7'), 7.27(1H,d,J = 1.5Hz,H-4),7.57(1H,d,J = 2Hz,H-12), 7.58(1H,t,J = 8Hz,H-6'), 7.81(1H,d,J = 2Hz,H-16), 7.84(1H,s,H-2'), 8.57(1H,dd,J_1 = 8,J_2 = 1Hz,H-5'), 11.26(1H, br s,O$\underline{H}$), 12.02(1H,br s, N$\underline{H}$). ^{13}C NMR(C_5D_5N):δ9.8(Me-3), 18.5(C-10), 55.9,56.4,56.5(3xOCH_3), 103.4(OCH_2O), 105.1(c-6), 106.0(C-2'), 109.6,,109.7(C-4,C-12), 111.5(C-7'), 112.6(C-4a'), 113.2(C-9'), 121.0(C-1'), 121.8(C-5'), 122.4(C-16), 124.4(C-9), 125.6(C-4b'), 126.1(C-6'), 127.9(C-11), 129.0(C-15), 132.3)C-8), 133.8(C-3a), 134.3(C-5), 136.1(C-10'), 142.6(C-7a), 145.6(C-7), 146.6(C-14), 147.7(C-4'), 148.6(C-13), 149.0(C-3'), 152.2(C-2), 158.8(C-8'), 169.7(CO). EIMS m/z (rel.int.): 615[M]$^+$(100), 584(12), 583(11), 308(25), 292(14), 285(10).

14-O-α-Cadinyl-eupomatenoid-7 (Compound 28)

Oil (3.5 mg). TLC:R_f0.78(S-1); anisaldehyde:grey. [α]$_D$ + 39°(C.O.3). IRν_{max} cm^{-1}:3019,2917,1614,1599,1505,1481,1450. UV λ_{max} nm(logϵ): 235(4.45), 265(4.48), 311(4.39). ^{1}H NMR:δ0.77(3H,d,J = 7Hz,Me-13' or Me-14'), 0.90(3H,d,J = 7Hz,Me-13' or Me-14'), 1.25(3H,s,Me-15'), 1.71(3H,s,Me-11'),

1.92(3H,dd,J_1=6.5,J_2=1.5Hz,Me-10), 2.43(3H,s,Me-3), 3.90(3H,s,OMe-13), 4.04(3H,s,OMe-7), 5.53(1H,br s,H-4'), 6.22(1H,dq,J_1=16,J_2=6.5Hz,H-9), 6.51(1H,dq,J_1=16,J_2=1.5Hz,H-8),6.83(1H,d,J=2Hz,H-6),7.04(1H,d,J=8Hz,H-15), 7.05(1H,d,J=2Hz,H-4), 7.26(1H,dd,J_1=8,J_2=2Hz,H-12), 7.32(1H,d,J=2Hz,H-16). ^{13}C NMR:δ9.7(Me-3), 15.1(Me-13'), 18.4(Me-10), 18.5(Me-15'), 21.5(Me-14@), 21.9(C-9'), 23.1(C-1'), 23.9(Me-11'), 25.9(C-12'), 31.0(C-2'), 37.7(C-8'), 40.2(C-5'), 46.3(C-6'), 48.0(C-10'), 55.8,56.1(2xOMe), 84.9(C-9'), 104.7(C-6), 109.2(C-4), 110.9(C-12), 111.8(C-3), 119.2(C-16), 122.4(C-4'), 124.4(C-9), 125.8(C-15), 127.1(C-11), 131.5(C-8), 133.1(C-3a), 133.7(C-5), 135.2(C-3'), 142.3(C-7a), 144.9(C-14), 151.4(C-2), 154,5(C-13). DCIMS m/z (rel.int.):529[M+H]$^+$(41), 528(14), 367(16), 326(11), 325(51), 324(100), 206(15), 205(93), 203(6).

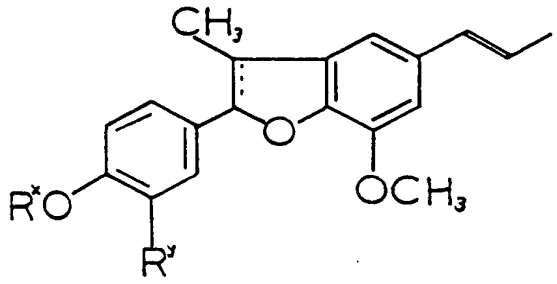
(2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone (Compound 34) Amorphous (17 mg). TLC:R_f0.44(S-1); anisaldehyde:yellow. $[\alpha]_D$-39°(c.01). CDλ_{max} nm($\Delta\epsilon$):220(+3.74), 270(-2.09), 295(+3.52), 315(-143). IRν_{max} cm^{-1}:3496(OH), 3016,1674,(CO),1609,1497. UV λ_{max} nm(logϵ):225(4.12), 274(4.09). ^{1}H NMR(250 MHz):δ1.46(3H,d,J=6.5Hz,Me-e), 176(1H,ddd,J_1=13.5, J_2=J_3=12.5Hz, H-3$_{ax}$), 2.21(3H,br s,Me-7), 2.48(1H,ddd,J_1=12.5, J_2=J_3=5.5Hz,H-3$_{eq}$), 3.16(1H,m,H-4), 3.91(3H,s,OMe), 4.33(1H,dd,J_1=13.5, J_2=5.5Hz,H-2$_{ax}$), 6.77(1H,br s,H-5), 7.84(1H,br d,J=1Hz,H-8).
^{13}C NMR(60MHz):δ15.7(Me-7), 20.5(Me-4), 31.6(C-4), 40.8(C-3), 55.5(OMe), 73.0(C-2), 107.0(C-5), 122.8(C-8a), 126.1(C-7), 129.7(C-8), 149.0(C-4a), 162.9(C-6), 198.5(CO). EIMS m/z (rel.int.):220[M]$^+$(68), 202(25), 177(19), 176(100), 175(61), 174(31), 159(12), 148(33), 147(14), 133(37), 117(14), 115(13).

EXAMPLE 2

DETERMINATION OF MUTAGENIC AND ANTIMUTAGENIC ACTIVITY

The four major constituents of the benzene extract from *Aristolochia taliscana* roots - eupomatenoid-7 (**7**), eupomatenoid-1 (**8**), eupomatenoid-8 (**17**), Licarin-A (**16**) - were tested for their mutagenic and antimutagenic properties using the Ames bio-assay (Maron, D.M. and Ames, B.N., Mutation Research, 1983, **113**,

173). The test compounds have the following structural formula:



Eupomatenoid-1: R^x & R^y = OCH_2O, dotted line = double bond
Eupomatenoid-7: R^x = OH, R^y = OCH_3, dotted line = double bond
Eupomatenoid-8: R^x & R^y = OCH_2O, dotted line = single bond
Licarin-A: R^x = OH, R^y = OCH_3, dotted line = single bond

Method

Salmonella typhimurium strain TA 100 was used as the test organism and 2-amino-anthracene (2-AA) and 2-nitrofluorene (2-NF) as standard mutagens, of which 1μg were added to each test plate. In the experiments with 2-AA, "S9 Mix" (derived from phenobarbital treated rat liver cells (De Flora, S., Camoirana, A., D'Agostini, F. and Balansky, R., Mutation Research, 1992, **267**, 183) was also added.

Results

None of the tested substances showed any mutagenic activity. Eupomatenoid-7 (**7**) exhibited strong antimutagenic effects against 2-aminoanthracene as well as against 2-nitrofluorene (Tab. 4). Licarin-A (**16**) and eupomatenoid-1 (**8**) were found to be antimutagenically active only in the experiment against 2-AA but not against 2-NF (Tab. 5). However, eupomatenoid-8 (**17**) did not show any antimutagenic effect in the test systems used (Tab. 6).

Eupomatenoid-7 (7)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for:	
	2-AA	2-NF
50	4	16
100	0	0

Table 4: Results from the experiments on antimutagenic activity of eupomatenoid-7 (7).

(±)-Licarin-A (6)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for	
	2-AA	2-NF
50	31	94
100	6	85

Table 5: Results from the experiments on antimutagenic activity of (±)-licarin-A (6)

Eupomatenoid-1 (8)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for	
	2-AA	2-NF
50	49	99
100	44	93

Table 6: Results from the experiments on antimutagenic activity of eupomatenoid-1 (8)

Eupomatenoid-8 (17)

Amount of compound added [μg]	Residual mutagenic activity (%) observed for	
	2-AA	2-NF
50	90	100
100	73	95

Table 7: Results from the experiments on antimutagenic activity of eupomatenoid-8 (17).

EXAMPLE 4
CYTOTOXICITY STUDIES

The cytotoxicity of compounds isolated from *Aristolochia Taliscana* was assayed using the well known brine shrimp bioassay. The cytotoxicities of compounds of the invention, expressed as percentage "death rates" after 24 hours, at varying concentrations, are shown in Table 8 below.

Table 8: Cytotoxicities of Compounds in the Brine Shrimp Assay

SUBSTANCE	"Death Rate" After 24 Hours (%)			LC_{50} (ppm)
	10ppm	100ppm	500ppm	
Aristolactam B (**3**)	5	9	29	>500
Aristolactam C (**4**)	0	0	3	>500
Eupomatenoid-7 (**7**)	27	38	38	>500
Eupomatenoid-1 (**8**)	12	16	20	>500
Licarin-A (**16**)	93	93	96	<10
Eupomatenoid-8 (**17**)	9	27	42	>500
Dihydrocarinatidine (**21**)	26	53	80	ca. 120
Coniferyl alcohol (**29**)	0	0	15	>500
Vanillin (**31**)	5	0	12	>500
Compound 34	52	86	100	<10
E-Germacrene D (**38**)	0	39	100	ca. 126
Podophyllotoxin	74	93	100	<10

EXAMPLE 5

ANTIFUNGAL ACTIVITY

The antifungal activities of compounds of the invention was determined using a plate diffusion method. Plates containing medium and a fungal species were made up and 150 microgramme aliquots of a test compound of the invention were spotted onto the plate. The diameter of inhibition of fungal growth around the test compound was then determined. The results of the tests are shown in Table 9 below.

Table 9: Antifungal Activity

	Test Microorganism		
COMPOUND	***Botryis cinerea***	***Rhizoctonia solani***	***Saprolegnia asterophora***
Aristolactam B (3)	-	+	-
Aristolactam C (4)	+	+	+ +
Eupomatenoid-7 (7)	-	-	-
Eupomatenoid-1 (8)	-	-	-
Licarin-A (16)	-	+ +	-
Eupomatenoid-8 (17)	-	-	-
Dihydrocarinatidine (21)	+	+	+
Coniferyl alcohol (29)	-	-	-
Vanillin (31)	-	-	-
Compound 34	+ +	+ +	+ +
E-Germacrene D (38)	+	+	-
- = no inhibition + = 5mm diameter inhibition + + = 5-10mm diameter inhibition			

CLAIMS

1. The use of an extract from *Aristolochia taliscana* or one or more anti-mutagenically active compounds isolable therefrom for the manufacture of a medicament for the treatment of disease states mediated by mutagenesis.

2. The use of an extract from an *Aristolochia* species such as *Aristolochia taliscana* or one or more component compounds isolable therefrom for the manufacture of a medicament for the treatment of chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, synovitis and psoriasis.

3. The use of an extract from *Aristolochia taliscana* or one or more antifungally active compounds isolable therefrom for the manufacture of a composition for antifungal use, for example in the treatment of fungal infections in animals, or for use in the treatment of fungal infections in plants.

4. The use according to any one of claims 1 to 3 wherein the composition contains at least 10%, preferably at least 20%, and more preferably at least 25% by weight of a phenylbenzfuran.

5. The use according to claim 4 wherein the phenylbenzfuran is a eupomatenoid.

6. The use according to claim 4 or claim 5 wherein the phenylbenzfuran contains a phenolic group.

7. The use according to claim 6 wherein the phenylbenzfuran is eupomatenoid-7.

8. The use according to any one of the preceding claims wherein the composition contains Licarin-A.

9. The use according to any one of the preceding claims wherein the

composition contains a cytotoxic tetralone compound.

10. The use according to any one of the preceding claims wherein the composition contains a 2-hydroxy-1-tetralone compound.

11. The use according to claim 9 or claim 10 wherein the tetralone compound is (2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone.

12. The use according to any one of the preceding claims wherein the composition contains at least 25% by weight of a phenolic eupomatenoid compound (such as eupomatenoid-7), at least 8% of Licarin-A and at least 8% of a non-phenolic eupomatenoid compound (such as eupomatenoid-8).

13. The use according to any one of the preceding claims wherein the composition contains an aristolactam.

14. The use according to any one of the preceding claims wherein the extract has been prepared by extraction of plant material from the *Aristolochia* species with an organic solvent.

15. The use according to claim 14 wherein the organic solvent is an alcoholic solvent such as ethanol or methanol or a mixture thereof.

16. The use according to claim 14 wherein the organic solvent is benzene, the solvent having been removed from the extract prior to use.

17. A method of treating a disease state mediated by mutagenesis, which method comprises administering to a patient suffering from said disease state an effective antimutagenic treatment amount of an extract from an *Aristolochia* species or one or more antimutagenic compounds isolable therefrom, as defined in any one of the preceding claims.

18. A method of inhibiting mutagenesis in an organism, which method comprises administering to the organism an effective antimutagenic amount

of an extract from *Aristolochia taliscana* or one or more antimutagenic compounds isolable therefrom, as defined in any one of the preceding claims.

19. A method of producing a cytotoxic effect in an organism (such as an animal), which method comprises administering to the organism in an amount effective to produce the cytotoxic effect an extract from *Aristolochia talscana* or one or more cytotoxic compounds isolable therefrom, as defined in any one of the preceding claims.

20. A method of preventing or treating a fungal infection in an animal patient such as a human, which method comprises administering to the patient an effective antifungal amount of an extract from *Aristolochia taliscana* or one or more antifungal compounds isolable therefrom, as defined in any one of the preceding claims.

21. A method of preventing or treating a fungal infection in a plant, which method comprises administering to the plant an effective antifungal amount of an extract from *Aristolochia taliscana* or one or more antifungal compounds isolable therefrom, as defined in any one of the preceding claims.

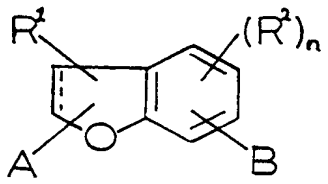
22. A method of inhibiting fungal growth in a substrate, which method comprises administering to the substrate an antifungal effective amount of an extract from *Aristolochia taliscana* or one or more antifungal compounds isolable therefrom, as defined in any one of the preceding claims.

23. A method according to claim 22 wherein the substrate is selected from animal (e.g. mammals such as humans) and plant tissues.

24. A method of treating a chronic inflammatory disease such as inflammatory bowel disease, rheumatoid arthritis, synovitis or psoriasis in a patient, which method comprises administering to the patient an effective amount of an extract from an *Aristolochia* species such as *Aristolochia taliscana* or one or

more component compounds isolable therefrom.

25. The use of a compound for the manufacture of a medicament for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the treatment of chronic inflammatory conditions, the compound being of the formula (I):



(I)

wherein the dotted line signifies a single or double bond; n is 0, 1, 2 or 3; A is a monocyclic aryl ring optionally substituted by one or more substituent groups which may be the same or different and are selected from R^3O, R^3, R^3S, halogen; aryl and heteroaryl, wherein R^3 is hydrogen, or a hydrocarbyl group optionally substituted by a hydroxy or hydrocarbyloxy group; B is selected from carboxy, carboxaldehyde, hydrocarbyl and hydrocarbyloxy groups wherein the hydrocarbyl group is acyclic or cyclic, and optionally contains one or more heteroatoms, and is optionally substituted by one or more hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aldehyde, alkanoyl, acetal, hemiacetal and carboxy groups; R^1 is hydrogen or a hydrocarbyl group optionally including one or more heteroatoms and optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups; and R^2 is hydroxy or a hydrocarbyl or hydrocarbyloxy group optionally substituted by one or more substituents selected from hydroxy, hydrocarbyloxy and aryl groups.

26. The use according to claim 25 wherein the monocyclic aryl ring A is attached to the 2-position of the furan ring.

27. The use according to claim 25 or claim 26 wherein the aryl ring is a phenyl group.

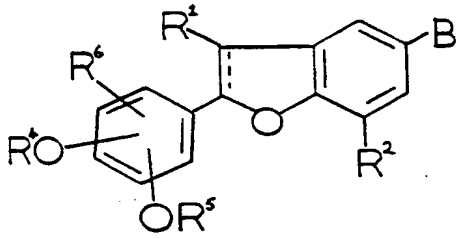
28. The use according to any one of claims 25 to 27 wherein the group B is attached to the 5-position of the benzofuran group.

29. The use according to any one of claims 25 to 28 wherein there is only one group R^2.

30. The use according to claim 29 wherein the group R^2 is attached to the 7-position of the benzofuran ring.

31. The use according to any one of claims 25 to 30 wherein the dotted line signifies a double bond.

32. The use according to claim 25 wherein the compound of the formula (I) has the formula (II):



(II)

wherein B, R^1 and R^2 are as defined in any one of claims 25 to 31, R^4 and R^5 are the same or different and each is selected from hydrogen, C_{1-20} hydrocarbyl, C_{5-20} aryl, or C_{5-20} oxygen-containing heteroaryl; R^6 is selected from hydrogen, halogen, C_{1-20} hydrocarbyl or C_{1-20} hydrocarbyloxy optionally substituted by one or more hydroxy, alkoxy, aralkyloxy groups; or R^6 is C_{5-25} aryl or oxygen or nitrogen-containing heteroaryl.

33. The use according to claim 32 wherein B is C_{1-6} alkyl or alkenyl optionally substituted by one or more substituents selected from hydroxy, CHO, or R^7O wherein R^7 is a C_{1-6} alkyl or alkenyl group.

34. The use according to claim 33 wherein the group B is selected from $CH=CHCH_3$, $CH_2CH=CH_2$, $CH(OH)CH=CH_2$, $CH=CHCHO$, CHO, $CH=CHCH_2OH$ and $CH(OH)CH(OH)CH_3$.

35. The use according to claim 34 wherein B is $CH=CHCH_3$.

36. The use according to any one of claims 25 to 35 wherein R^4 and R^5 are selected from hydrogen, or C_{1-6} alkyl, or R^4 and R^5 together define an alkylene group such as $-CH_2-$.

37. The use according to claim 36 wherein at least one of R^4 and R^5 is hydrogen.

38. The use according to any one of claims 32 to 37 wherein R^6 is selected from hydrogen, halogen, C_{1-6} alkoxy (e.g.methoxy), a 2-benzofuranyl ring, and an aristolactam group.

39. The use according to any one of claims 25 to 38 wherein each hydrocarbyl group is selected from aliphatic, alicyclic and aromatic groups.

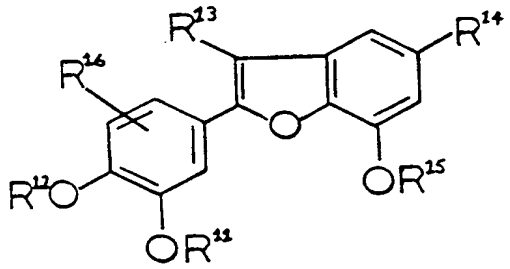
40. The use according to claim 39 wherein the hydrocarbyl group is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, aryl, aralkyl, aralkenyl, aralkynyl, optionally interrupted by one or more heteroatoms such as oxygen and sulphur.

41. The use according to claim 40 wherein the hydrocarbyl group is a C_{1-6} alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl; a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycloheptanyl, decalinyl, adamantyl, norbornyl and bicyclooctyl; an alkenyl or alkynyl groups selected from vinyl, ethynyl, allyl, 1-propenyl, propargyl, but-1-enyl, but-2-enyl, but-3-enyl and 3-methylbutenyl; a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl and cycloheptenyl; an aryl groups selected from phenyl and naphthyl; or a phenylalkyl or phenylalkenyl groups selected from benzyl, phenethyl, phenylpropyl, phenylbutyl and styryl groups.

42. A compound of the formula (I) or (II) as defined in any one of the preceding claims for use in medicine, for example for use in any one or more of the therapeutic uses selected from the treatment of neoplastic diseases or diseases mediated or initiated by mutagenesis or abnormal cellular proliferation, or as a cytotoxic agent, or the treatment of chronic inflammatory conditions, or as an anti-fungal agent in the treatment of fungal infections in plants or animals; but provided that when R^1 is 3-methyl, R^2 is a single methoxy group at the 7-position, and either (i) the furan ring is unsaturated and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group or a 3,4-methylenedioxyphenyl group; or (ii) the furan ring is a 2,3-dihydrofuran ring and is substituted at the 2-position with a 4-hydroxy-3-methoxyphenyl group, then B is other than a prop-1-enyl group attached to the 5-position of the benzfuran ring.

43. A pharmaceutical composition comprising a compound of the formula (I) or (II) as defined in claim 42 together with a pharmaceutically acceptable carrier.

44. A compound of the formula (III):



wherein R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} is selected from hydrogen, C_{1-6} alkyl; a cyclic terpenoid group or a group of the formula E, G or J;

R^{13} is selected from hydrogen; C_{1-3} alkyl or hydroxy-C_{1-3} alkyl;

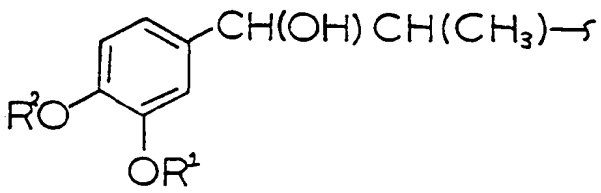
R^{14} is selected from $CH=CH\text{-}CH_3$, $CH(OH)CH=CH_2$, $CH=CH\text{-}CHO$,

CH=CH-CH_2OH, CH(OH)CH(OR^{17})CH_3, or a group L;

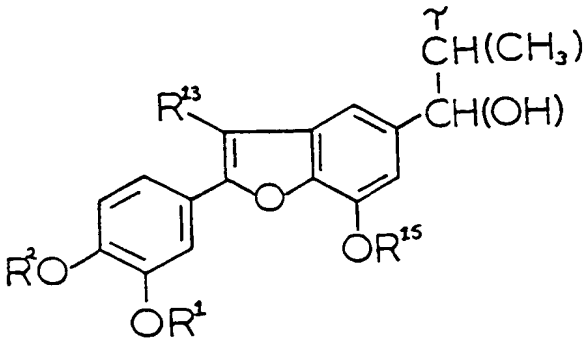
R^{15} is hydrogen or C_{1-6} alkyl;

R^{16} is hydrogen, a group M or an aristolactam group; and

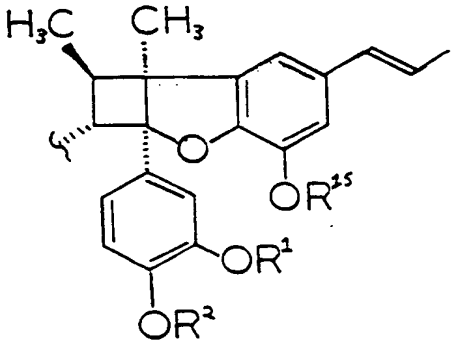
R^{17} is hydrogen or a group T; wherein the groups E, G, L, J, M and T are represented by the formulae:



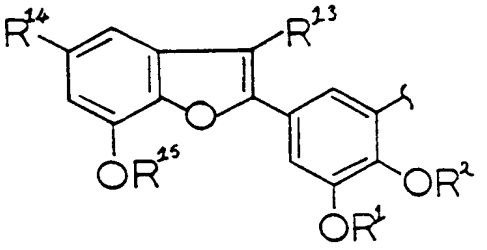
(E)



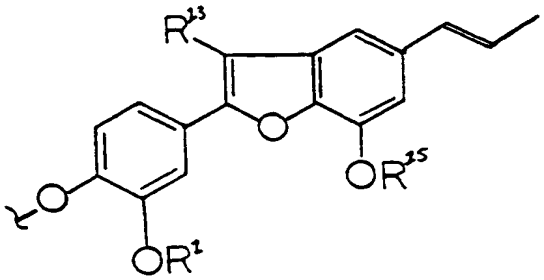
(G)



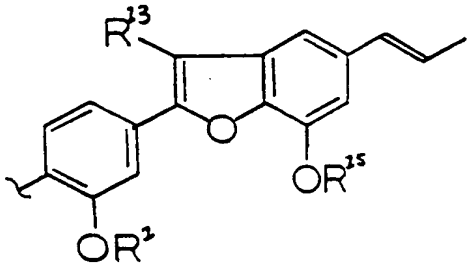
(L)



(J)



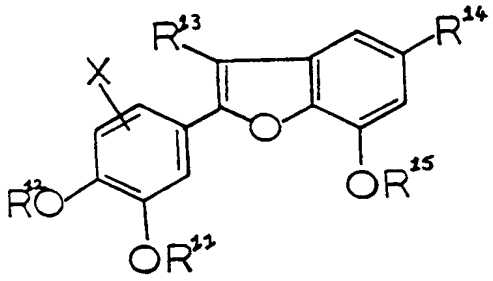
(M)



(T)

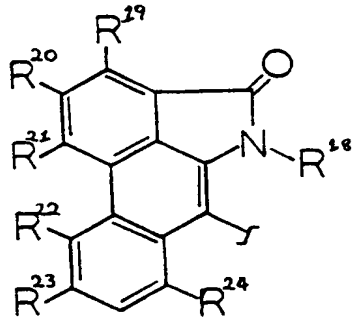
and pharmaceutically acceptable salts thereof, provided that when R^{11}, R^{13} and R^{15} are all methyl,and R^{12} and R^{16} are both hydrogen, R^{14} is selected only from $CH(OH)CH=CH_2$, $CH=CH\text{-}CHO$, $CH=CH\text{-}CH_2OH$, $CH(OH)CH(OR^{17})CH_3$ where R^{17} is a group T, or a group L.

45. A compound of the formula (IV):



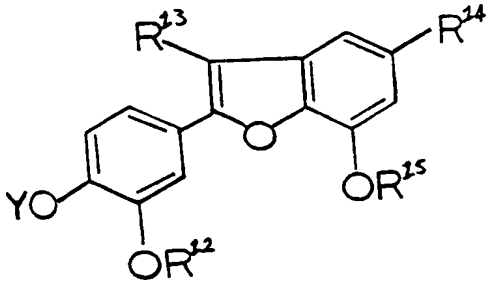
(IV)

wherein R^{11}, R^{12}, R^{13} R^{14}, R^{15} and R^{17} are as defined in claim 25 and X is a group:



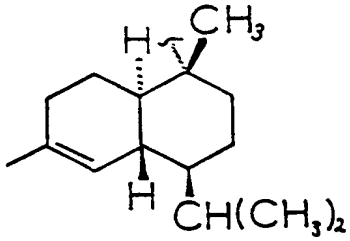
wherein R^{18} is hydrogen, benzyl or C_{1-6} alkyl; R^{19} to R^{24} are the same or different and are selected from hydrogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl and hydroxy-C_{1-6} alkyl; or any two adjacent groups together form an alkylene dioxy group.

46. A compound of the formula (V):

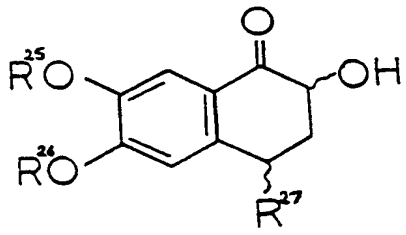


(V)

wherein Y is a monocyclic or bicyclic terpenoid group and in particular a group of the structure:



47. A tetralone compound of the formula (VI):



wherein R^{25} and R^{27} are the same or different and each is C_{1-6} alkyl; and R^{26} is hydrogen or C_{1-6} alkyl, or R^{25} and R^{26} together form an alkylene-dioxy group.

48. A compound according to claim 48 wherein R^{25}, R^{26} and R^{27} are all methyl.

49. A compound according to claim 47 or 48 for use as a biocide.

50. A compound according to claim 49 for use in the treatment of fungal infections, or for use in the treatment of cancers and other proliferative diseases such as psoriasis.

51. A compound selected from the group consisting of:
(±)-5-(1-Hydroxyallyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran;
2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran;
2-(4-Hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(E)-3-oxopropenyl]benzofuran;
5-Formyl-3-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran;
2-(4-Hydroxy-2-methoxyphenyl)-5-[(E)-3-hydroxypropenyl]-7-methoxy-3-methylbenzofuran;
2-(3,4-Dihydroxyphenyl)-7-methoxy-3-methyl-5-(E)-propenylbenzofuran;
erythro-5-(1,2-Dihydroxypropyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran;
(2R,3R)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(E)-propenylbenzofuran;
erythro-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propylacetate;
threo-1-(4-Acetoxy-3-methoxyphenyl)-2-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propyl-acetate;
threo-1-[2-(4-Hydroxy-3-m ethoxyphenyl)-7-methoxy-3-methylbenzofuran-5-yl]-2-[4-(3-methyl-5-(e)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]propan-1-ol;
2-Methoxy-4-[7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl]-6-[4-(7-methoxy-3-methyl-5-(E)-propenylbenzofuran-2-yl)-2-methoxyphenoxy]phenol;
8.2',9.3'-Tetrahydro-bis-eupomatenoid-7;
15-(Aristolactam-I-9-yl)-eupomatenoid-7;
14-O-α-Cadinyl-eupomatenoid-7; and
(2R,4S)-2-Hydroxy-6-methoxy-4,7-dimethyl-1-tetralone.

52. A pharmaceutical composition comprising a compound as defined in any one claims 44 to 51 together with a pharmaceutically acceptable carrier.

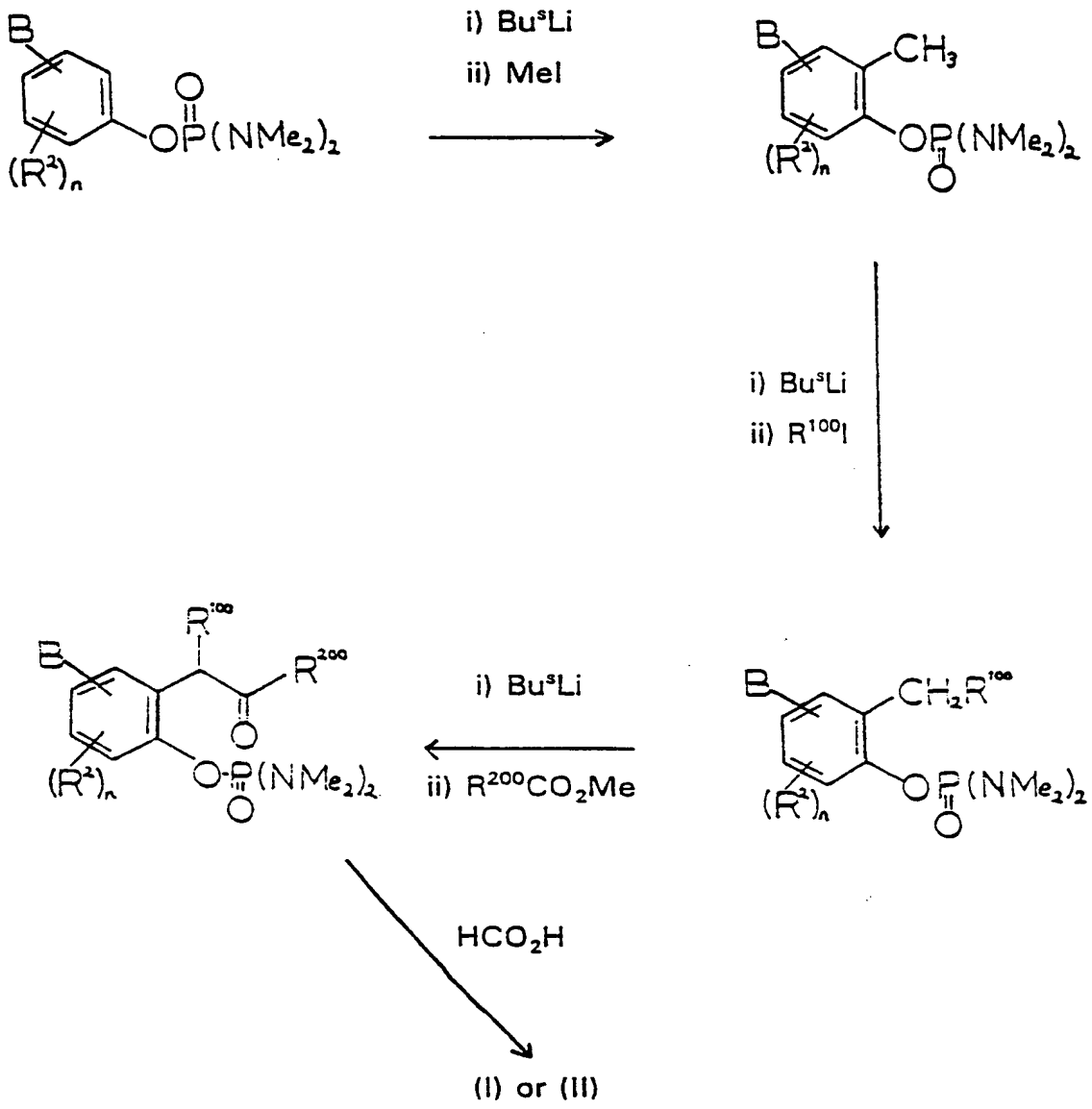

i) Bu^{s}Li
ii) MeI
i) Bu^{s}Li
ii) R^{100}I
i) Bu^{s}Li
ii) R^{200}CO$_2$Me
HCO$_2$H
(I) or (II)

Figure 1

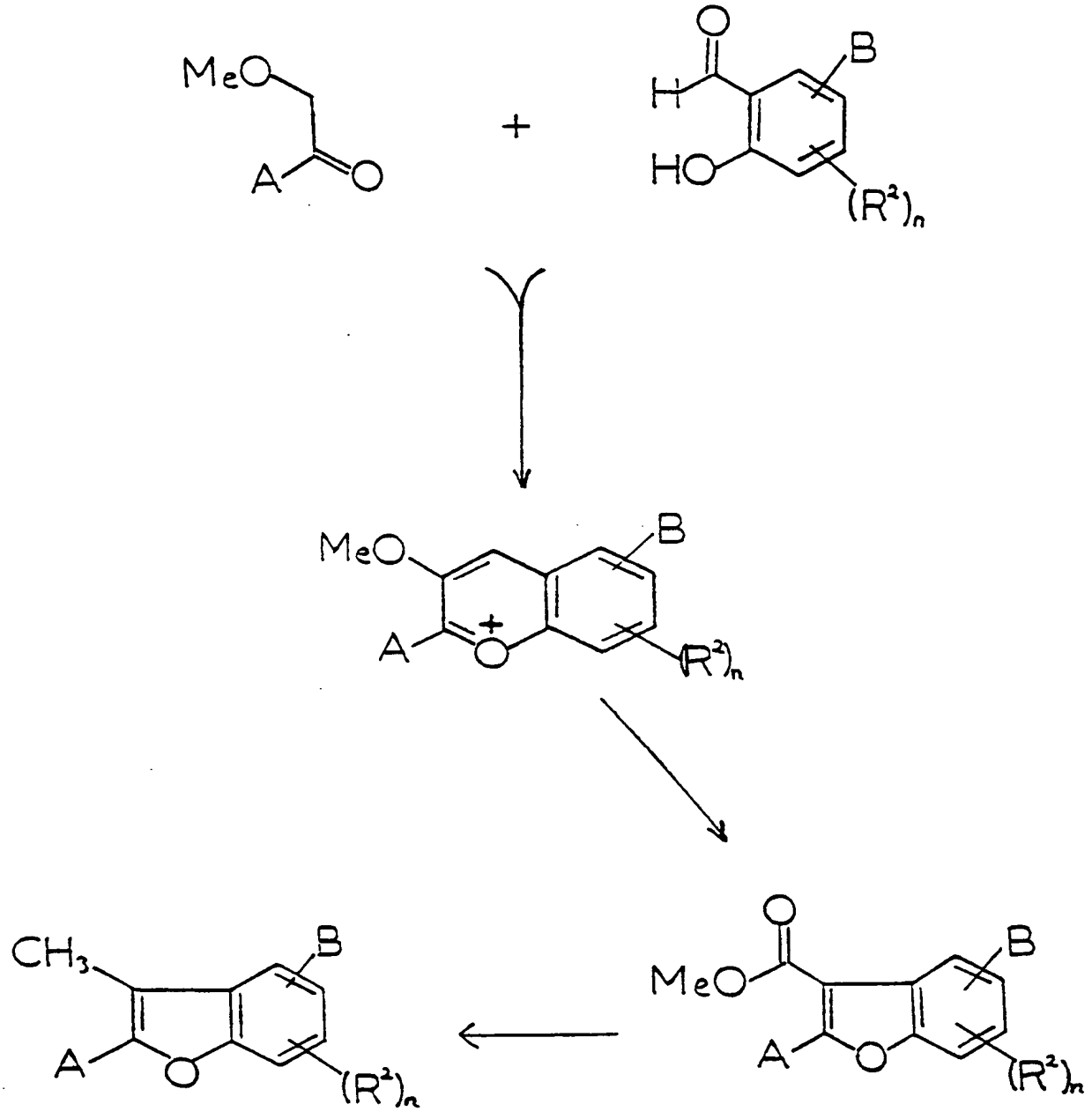


Figure 2

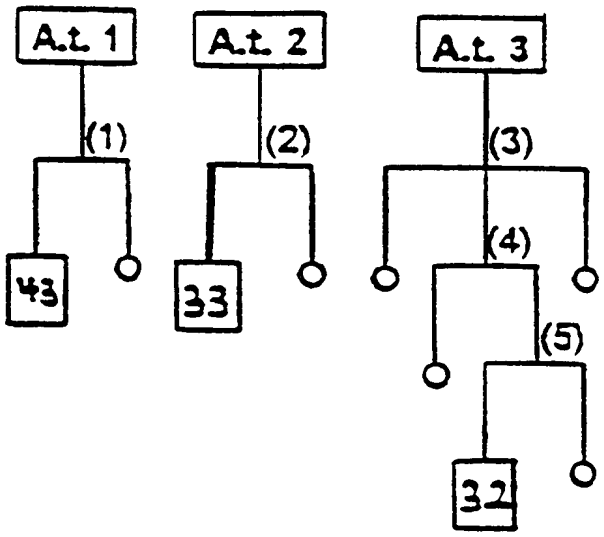
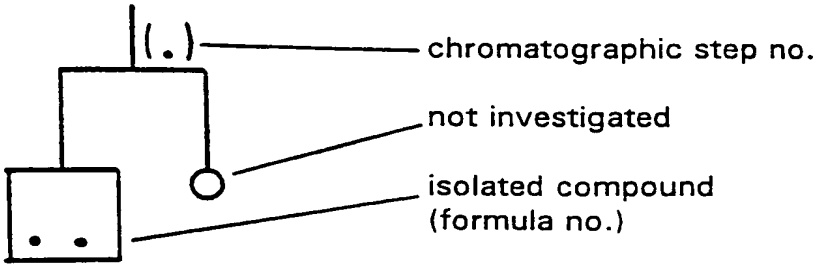


Figure 3

KEY TO DIAGRAMS



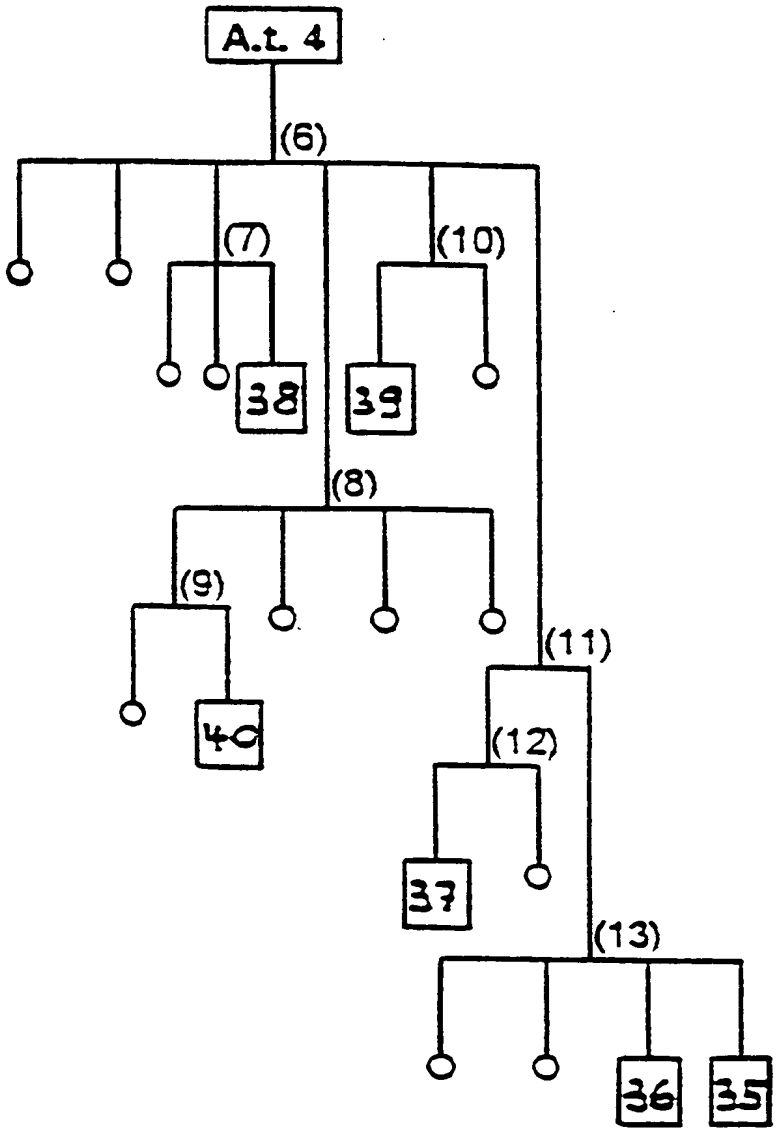


Figure 3 Continued

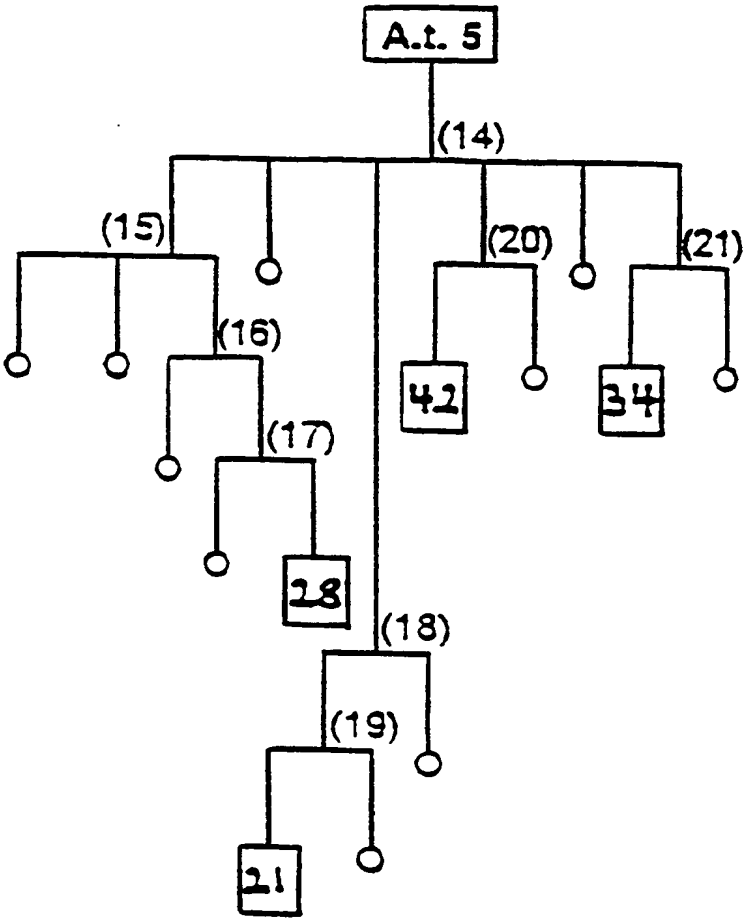


Figure 3 Continued

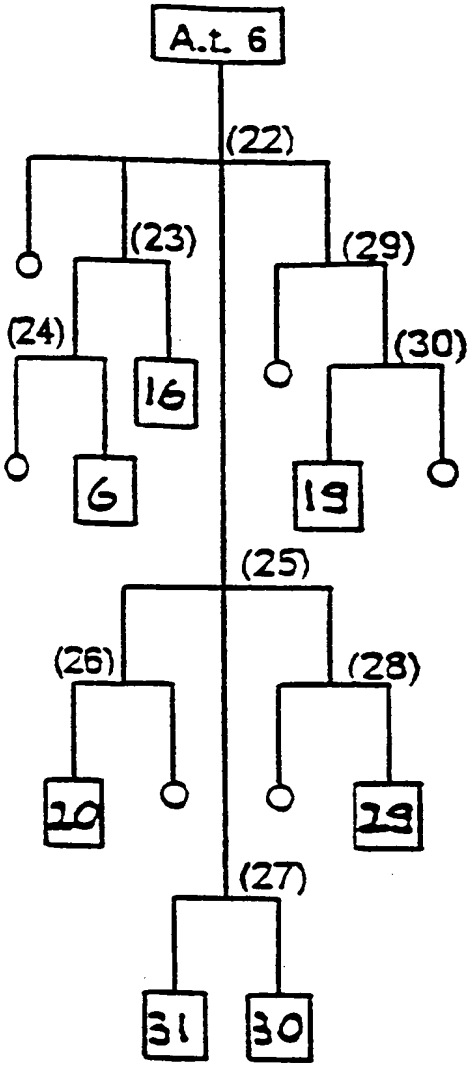


Figure 3 Continued

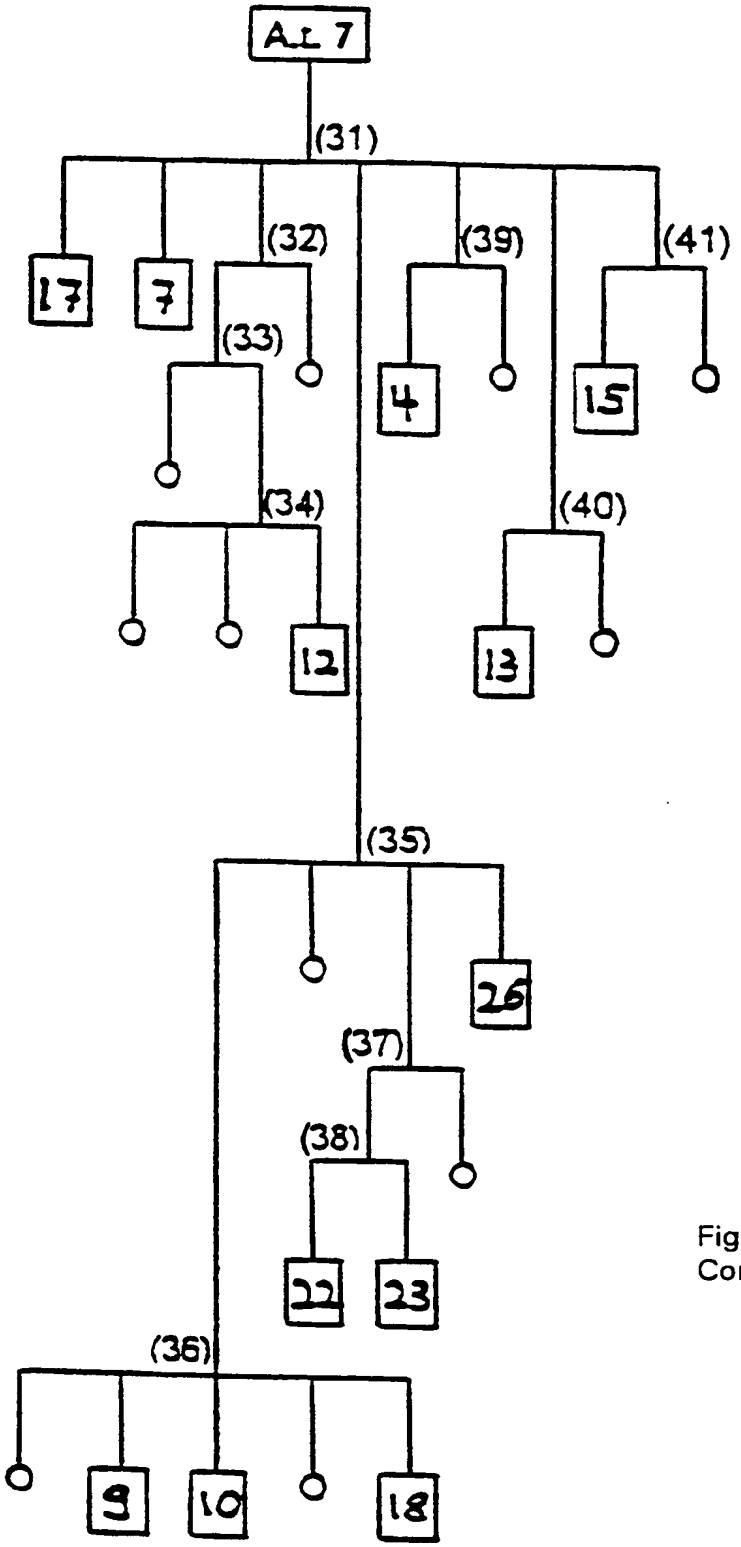


Figure 3
Continued

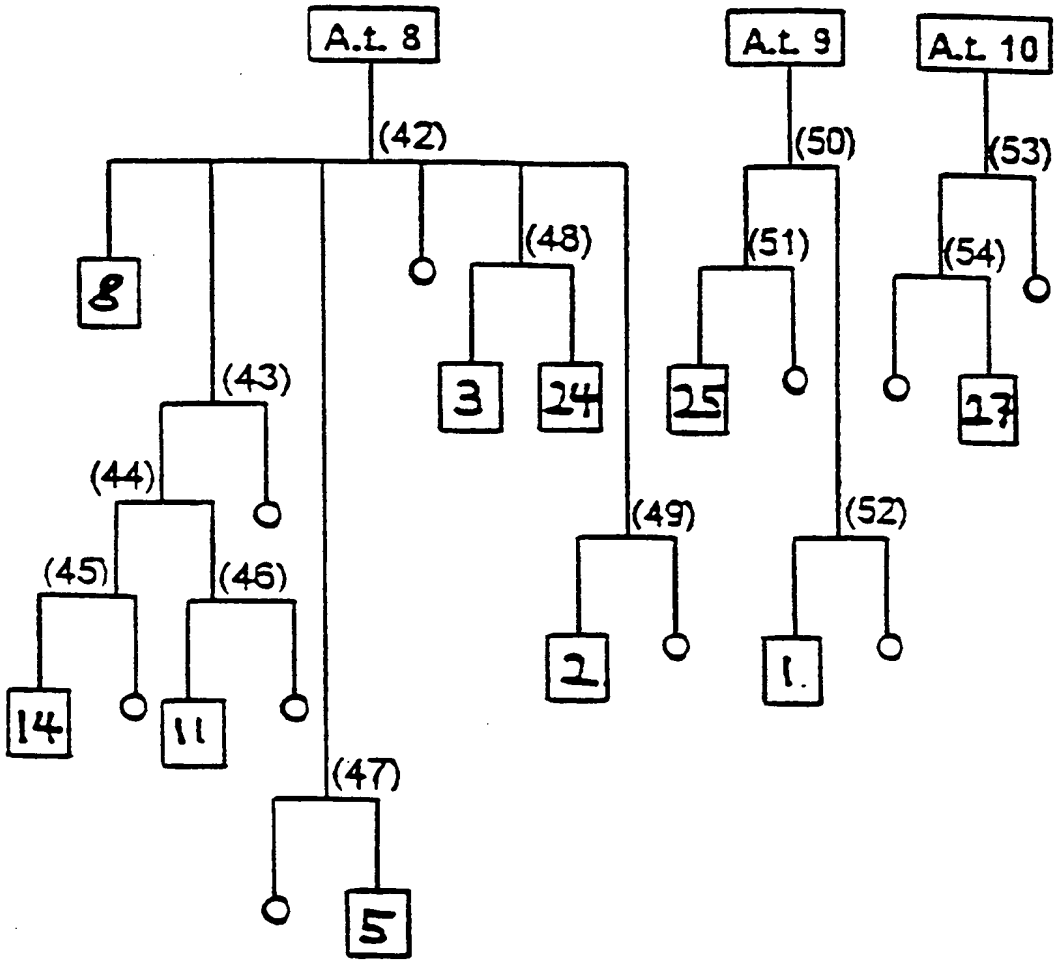


Figure 3 Continued